Sildenafil Citrate and Uteroplacental Perfusion in Fetal Growth Restriction

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ABSTRACT

Background: Severe early-onset fetal growth restriction can lead to a range of adverse outcomes including fetal or neonatal death, neurodisability, and lifelong risks to the health of the affected child. Sildenafil, a phosphodiesterase type 5 inhibitor, potentiates the actions of nitric oxide, which leads to vasodilatation of the uterine vessels and might improve fetal growth in utero.

Objective: To evaluate effectiveness and safety of Sildenafil citrate for treatment of intrauterine growth restriction (IUGR). **Design:** A prospective randomized control study.

Setting: At Ain shams University hospital and Kafr Aldwwar main Hospital in El-Beheria governorate.

Subjects: Eighty pregnant women with gestational age between 24 and 34 weeks having singleton pregnancy and suffering from IUGR attending an antenatal clinic.

Methods: Eighty pregnant women with FGR and abnormal umbilical artery Doppler between 24and34 weeks were randomly allocated to sildenafil (n= 40) 25mg tid or placebo (n=40) with a plenty of fluids until delivery.

Main outcome measure: Length of pregnancy, neonatal weight and ICU admission.

Results: Sildenafil treatment was associated with a significant increase in length of pregnancy ($P< 0.05$) and a significant increase in estimated fetal weight by ultrasound ($P<0.05$), and was associated with a significant decrease in neonatal ICU admission ($P=0.218$) and neonatal mortality ($P=0.290$).

Conclusion: Sildenafil citrate can improve utero-placental perfusion and length of pregnancy in pregnancies complicated by IUGR. It appears to have a significantly positive effect on fetal weight. Sildenafil treatment may offer a new opportunity to improve perinatal outcomes, for pregnancies complicated by IUGR. However these observations require further studies on wide scale.

Keywords: Sildenafil Citrate, Uteroplacental Perfusion, Fetal Growth Restriction.

INTRODUCTION

Intrauterine growth restriction (IUGR) is a fetal weight that is below the10th percentile for gestational age as determined by ultrasound. This can also be called small for gestational age (SGA) or fetal growth Restriction (FGR)[1] , while ***Samangaya et al.*** [2] defined FGR as one or more of the following: fetal abdominal circumference <5th percentile. Amniotic fluid index < 5th percentile or Doppler umbilical artery pulsatility index > 95th percentile for gestational age. It affects up to 7-8% of all pregnancies [3, 4]. Fetal growth restriction (FGR) complicates 7-15% of pregnant women and in its early and severs form the risk of perinatal morbidity and mortality is increased [5].

Causes of FGR are classified to fetal factor as: chromosomal abnormalities, multiple pregnancies, fetal structural anomalies and fetal infections. Maternal factors as: hypertension anemia, diabetes mellitus, chronic lung diseases and heart. Placental factor as: Chorioangioma, infarction, circumvallate placenta, confined placental mosaicism, obliterative vasculopathy of placental bed [6].

Umbilical artery Doppler has been the mainstay for diagnosing placental insufficiency for 2 decades. Consequently, fetuses with normal UA Doppler, normally defined as small for gestational age (SGA), have long been considered to be constitutionally small fetuses with a good prognosis [7] Therefore, all Doppler indices of the umbilical artery can be used to distinguish between the high-risk small fetus that is truly growth-restricted and the lower-risk small fetus [8].

Several new vasodilator drugs have recently been suggested to augment blood flow to tissues, one of these drugs is sildenafil citrate (Viagra) [9].

Sildenafil citrate is a selective inhibitor of cyclic guanosine monophosphate (cGMP) formation through inhibition of type 5phosphodiesterase (PDE5) [9]. It increases uterine blood flow and potentiates estrogen-induced vasodilatation [10].

Several studies postulated that Sildenafil citrate may offer a potential therapeutic strategy to improve utero placental blood flow in FGR pregnancies [11. 12 &13].

AIM OF THE WORK

The aim of this study is to asses the efficacy of sildenafil citrate therapy in prolonging pregnancy in women with fetal growth restriction.

Research hypothesis

Sildenafil citrate may prolong pregnancy in women with fetal growth restriction and abnormal umbilical artery Doppler.

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Research Question

Does sildenafil citrate prolong pregnancy in women with fetal growth restriction and abnormal umbilical artery Doppler?

PATIENTS AND METHODS

Research Design

A prospective randomized clinical trial. The study was approved by the Ethics Board of Ain Shams University.

Research setting

The study was conducted at the Department of Obstetrics and Gynecology in Ain shams University Hospital and Kafr Aldwwar General Hospital in Elbeheira Governorate. And recruitment of cases started in September 2016 and ended in December 2017.

Population of the study

All pregnant women who attended outpatient clinic, presented in the emergency room, or those referred to the hospital from other place. Pregnant female diagnosed as SGA during u/s examination and Underwent umbilical artery Doppler velocimetry. Patient with decreased umbilical flow were submitted to:

1) Detailed complete history taking

2) Clinical Examination:

a. General examination b. Abdominal examination (Symphysis-fundal height)

3) Investigation

a. Ultrasound assessment to evaluate gestational age (GA), abdominal circumference (AC), fetal weight, amniotic fluid index (AFI).

b. Basal complete blood picture, blood serum creatinine, uric acid, aspartate transaminase, bilirubin, albumin, urine analysis and random blood sugar.

4) Fetal Doppler indices measurement.

For Umbilical vessels the following indices were measured:

- The Systolic/Diastolic (S/D) ratio.
- Resistance index (RI).
- Pulsatility index (PI).

All three indices are highly correlated. PI shows a linear correlation with vascular resistance as opposed to both S/D ratio and RI, which show a parabolic relationship with increasing vascular resistance. Abnormal umbilical artery Doppler indices were defined as S/D ratio greater than 2 and RI greater than 0.7, so all these pregnancies were the candidates of our study [14].

After evaluation the patient fulfilling the following CCC was included in the research.

Inclusion criteria:

- SGA fetus diagnosed by:
- Confirmed GA (1st day LMP- U/S).
- AC below 10th percentile.
- Reduced umbilical artery Doppler blood flow velocimetry.
- Regular menstrual pattern before pregnancy.
- Gestational age (GA) between 24-36 weeks.
- Singleton pregnancy.
- Ability to attend follow up as planned.

Exclusion criteria

- Normal or Reversed umbilical artery Doppler blood flow velocimetry.
- Uncertain gestational age.
- Maternal cardiovascular morbidity.
- Known or suspected fetal anomalies.
- Where urgent delivery is indicated.
- Usage of any vasodilator medication.
- Smoking.
- Drug or alcohol abusers.
- Obstetrical complications (intrauterine infection, bleeding, premature rupture of membranes).
- Follow up of the patient was difficult.

Patients fulfilled the inclusion and exclusion criteria were offered to share in the study after full explanation regarding study design and possibly expected benefits and risks, those who agreed should signed a special consent form.

Eighty pregnant women, suffering from intrauterine growth restriction (IUGR) with gestational age between 24-34 weeks as determined by the 1st day of last menstrual period and confirmed by ultrasound before the 20th week of gestation signed the consent.

Allocation and Concealment:

Eighty sequential numbered opaque sealed envelopes were numbered serially and in each envelope the corresponding letter which donates the allocated group was put according to randomization table then all envelopes were closed and put in one box. When the first patient arrived, the first envelope was opened and the patient was allocated to the letter inside.

Randomization:

Was done using computer generated randomization sheet using MepCalc software version 12.5.

Intervention:

Participants were randomized into one of the following drug regime:

Group (A): "sildenafil citrate group" included 40 patients that received a 25 mg tablet of sildenafil citrate orally. Umbilical artery Doppler velocimetry measured before and after 2 hours of sildenafil ingestion. If no significant side effects were recorded, the protocol was repeated 48 hours after the 1st tablet ingestion. In cases of positive and encouraging results and if no serious side effects are

detected, we used 25 mg sildenafil three times daily until delivery [15]. Each patient was instructed for bed rest and nutritional supplementation including excessive oral fluid intake around the time of each tablet ingestion with the aim of increase of amniotic fluid index [16]. Pregnancy was allowed to continue until fetal maturity as long as fetal growth continues and fetal evaluation remains normal.

Group (B): "placebo group": This group consisted of 40 women who received oral dose of placebo.

Blinding:

Both sildenafil and placebo tablets having an identical appearance. Both the care giver and the patient didn't know the nature of medication (Double blind study).

Follow up:

All patients were followed up by

1) Ultrasonic fetal growth assessment: Growth of bi-parietal diameter (BPD), head circumference (HC), AC, femur length (FL), HC/AC ratio, FL/AC ratio and EFW. If AC increases by at least 1cm / 2 weeks the growth is satisfactory. If it is less than 1cm/ 2 weeks or growth is arrested termination of pregnancy is recommended irrespective of the results of antenatal testing for fetal surveillance [17].

2) Umbilical Doppler velocimetry (for surveillance of fetal hypoxemia/ acidaemia):

- When umbilical artery end diastolic flow indices are normal it is reasonable to repeat surveillance every 14 days.
- When umbilical artery end diastolic flow indices are decreased and delivery is not indicated repeat surveillance twice weekly.
- When umbilical artery end diastolic flow indices are absent or reversed urgent delivery to be done [18].

3) Fetal lung maturity score as described by [19].

All patient were followed tell the end of the pregnancy and after delivery neonatal weight & neonatal care were evaluated.

Outcome Measures

Primary outcome measure:

1- Length of pregnancy.

Secondary outcome measures:

1- Neonatal birth weight.
2- Neonatal ICU admission.

Statistical analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric while qualitative data were presented as number and percentages.

The comparison between two independent groups with qualitative data was done by using ***Chi-square test*** and/or ***Fisher exact test*** only when the expected count in any cell found less than 5.

The comparison between two independent groups with quantitative data and parametric distribution was done by using ***Independent t-test.***

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: P > 0.05: Non-significant. P < 0.05: Significant. P < 0.01: Highly significant.

RESULTS

Table (1): Comparison between the two studied groups regarding base line gestational age and estimated fetal weight estimated by u/s on admission.

	Sildenafil Group "n=37"	**Placebo Group "n=36"**	**Test of significance**	**P-value**
Gestational age on admission				
Range	25-34	26-33	t=0.328	0.744
Mean ±S.D.	32.00±4.1	31.72±3.11		
Estimated fetal weight on admission			T=1.333	0.187
Range	900-1250	950-1200		
Mean ±S.D.	1060.0±122.6	1100.0±133.6		

Table (2): Comparison between the two studied groups regarding the gestational age at delivery.

Gestational age at delivery (weeks)	**Sildenafil Group "n=37"**	**Placebo Group "n=36"**
Range	36-40	34-39
Mean ±S.D.	38.2±1.36	37.4±1.42
T	2.459	
P	0.016*	

Table (3): Comparison between the two studied groups regarding the Birth weight (gm)

Birth weight (gm)	Sildenafil Group "n=37"	Placebo Group "n=36"
Range	1100-2850	1030-2680
Mean ±S.D.	2070.5±450.3	1842.2±352.0
T	2.409	
P	0.019*	

Table (4): Comparison between the two studied groups regarding the newborn ICU admission and mortality

	Sildenafil Group "n=37"		Placebo Group "n=36"		X^2	P-value
	No.	%	No	%		
Newborn ICU admission	2	5.4%	5	13.9%	1.515	0.218
Mortality	1	2.7%	3	8.3%	1.117	0.290

Table (5): Comparison between sildenafil group regarding the maternal complaints before and after treatment

	Before treatment		After treatment		X^2	p-value
	No.	%	No	%		
Headache	14	37.8%	29	78.4%	12.491	<0.001
Epigastric discomfort	16	43.2%	16	43.2%	0.000	1.000
Vomiting	2	5.4%	5	13.5%	1.42	0.233
Visual disturbance	2	5.4%	8	21.6%	4.163	0.041
Diarrhea	3	8.1%	5	13.5%	0.561	0.453
Irregular uterine Contractions	9	24.3%	6	16.2%	0.753	0.386
Painful uterine Contractions	3	8.1%	1	2.7%	1.057	0.303
Increase or change in vaginal discharge	13	35.1%	7	18.9%	2.467	0.116
Decreased fetal movements	4	10.8%	2	5.4%	0.725	0.394

In our study there was significant increase in **length of pregnancy** in sildenafil group compared to placebo group. The mean gestational age in sildenafil group were 38.2±1.36 weeks and in placebo group were 37.4±1.42 weeks (p =0.016), and **neonatal birth weight** was significantly increased in sildenafil group than placebo group. Mean birth weight in sildenafil group was 2070.5±450.3, while in placebo group was 1842.2±352.0 (p<0.05).

In addition there is significant decrease in **neonatal ICU admission and mortality** in sildenafil group than placebo group, in sildenafil group 2 cases admitted to ICU compared with 5 cases in placebo group (p=0.218), and only one IUFD in sildenafil group compared with three IUFDs in placebo (p=0.290).

Regarding **maternal safety**, sildenafil was well tolerated and no women withdraw from the study due to side effects.

Headache was the commonest side effect (78.4%) followed by visual disturbance and gastrointestinal tract symptoms.

DISCUSSION

To achieve optimal fetal growth, adequate blood flow in uteroplacental vascular function is essential. Abnormal vasculature adaptation, resulting in aberrant blood flow, has been implicated as a possible cause of fetal growth restriction (FGR). Sildenafil, as a vasodilator, should be an alternative in the treatment of Intra-Uterine-Growth-Retardation (IUGR) and preeclampsia by later normalization in velocimetric profile.

As a therapeutic agent in FGR gestations by promoting myometrial small artery vasodilatation, reducing in maternity peripheral resistance and increasing flow within the uteroplacental bed, can improve uteroplacental perfusion. PDE-5 inhibitors can reduce vasoconstriction and improve relaxation of FGR myometrial small arteries [2].

Parallel to our study case report study of pregnant female with IUGR and oligohydramnios received sildenafil citrate 25 mg vaginally twice a day started on 27 weeks gestation showed a consistent increase in fetal weight and AFI with sildenafil citrate without any adverse fetal outcome.

An elective cesarean section was done at 37th week for breech presentation, and a healthy female child of 2.3 kg was delivered. Baby cried immediately after birth, and Apgar score was 7/10 and 9/10 at 1 and 5 minutes, respectively. It increases the window of fetal maturity and hence reduces neonatal morbidity and mortality due to prematurity [20].

El-Sayed et al. [21] in a randomized controlled trial of 54 patients at 24 weeks or more complicated by FGR and abnormal Doppler indices were randomly allocated 1:1 into an intervention arm (receive sildenafil citrate, 50 mg) or a control arm (receive placebo). there was a significant pregnancy prolongation in sildenafil group, increased GA at delivery, mean GA at delivery for sildenafil and placebo was 32 + 2 and 30 + 5 weeks, respectively (with standard deviation of 12 days, p=0. 004), improved neonatal weight (p=. 0001), and found less admission to neonatal intensive care unit (7% and 30% of the cases required NICU admission, p< 0.03), not only the majority of these babies were preterm, but they were also FGR.

In sildenafil group mothers reported mild adverse reactions in the form of headache (3 patients), flushing (1patient), flushing with diarrhea (1 patient), while placebo group reported nausea (3 patients), all were self-limited with no needed treatment.

Trapani et al. [22] in a randomized control study of 100 cases with preeclampsia. found that sildenafil citrate given to women with preeclampsia with a severe feature at an oral dose of 50 mg every 8 hours allows the prolongation of pregnancy by an average of 4 days (14.4 days compared with 10.4 days, P=.008). We speculate that this prolongation may be the result of better control of blood pressure, improvement of maternal and fetal blood flow, or a combination of both. The medication was well tolerated. There was no difference in the incidence of adverse events between the groups. Only three patients suspended the medication as a result of possible side effects (severe headache): one in the study group and two in the control group**.**

In another Study of 100 pregnant women with severe early and late onset fetal growth restriction and oligohydramnios. Intervention included administration of Sildenafil citrate 25mg three times daily until delivery, found that sildenafil prolong the length of pregnancy. GA at delivery since LMP 30 to 36 weeks. Sildenafil treatment improved perinatal outcome by improving fetal growth velocity as assessed by serial AC measurements by ultrasound. There was improvement in AFI and fetal Doppler parameters (p<0.05). Sildenafil therapy reduced NICU admissions and mortality (98 live birth all discharged to home versus only 2 still birth) and 3 years follow up shows no effect on the overall development of the babies. Maternal side effect is almost negligible. Those who complained of head ache and palpitation the dose of Sildenafil was reduced from three times a day to two times a day. Therefore Sildenafil represent a novel intervention for the pregnancies with IUGR [23].

In another case control study of 27 pregnant females with FGR., Sildenafil citrate (25 mg three times daily until delivery) was given to 10 women another 17 women received placebo treatment. Sildenafil treatment was associated with increased post-eligibility fetal AC growth velocity [9/10 (treated) versus 7/17 (naive). odds ratio, 12.9 (95% CI, 1.3, 126)]. We also examined post-eligibility fetal growth velocity using individual pregnancies as their own controls com-pared with pre-eligibility growth velocity. Sildenafil therapy was associated with a significant increase in fetal growth velocity, expressed as equivalent daily AC growth [pre-eligibility median, 0.59 (interquartile range, 0.37, 0.79)., post-eligibility median, 0.94 (0.78, 1.39)., Wilcoxon P = 0.0039., n = 9), but remaining Sildenafil-naive was not [pre-eligibility median, 0.71 (0.48, 0.85)., post-eligibility median, 0.58 (0.38, 0.77)., Wilcoxon P = 0.2513., n = 17]. Both survival to, and intact survival at, hospital discharge tended to be more frequent in the fetuses/neonates exposed to Sildenafil in utero, there were no adverse maternal side-effects of medication reported in the treated group [24].

Panda et al. [11] a case control study of pregnant female with FGR, sildenafil citrate 50 mg tid was used. Doppler showed improved uteroplacental blood flow with estimated fetal weight of around 800 gm and hence pregnancy could be continued to another 3 weeks. A live male baby of 800 gr was delivered and shifted to Neonatal Intensive Care Unit (NICU) for further management. After 80 days of NICU care, the baby was finally discharged healthy with a weight of 2.3 kg. After 1 month of discharge, mother and infant came for follow up and both were doing perfectly well. Also, the infant was checked by pediatrician and was found healthy.

In contrary to our study ***Andrew et al.*** [25] a multicenter, randomized, placebo-controlled, double-blind trial done between Nov 21, 2014, and July 6, 2016, recruited 135 women and randomly assigned 70 women to sildenafil and 65 women to placebo. Found no difference in the median randomisation to delivery interval between women assigned to sildenafil (17 days [IQR 7–24]) and women assigned to placebo (18 days [8–28].,

p=0·23). Live births (relative risk [RR] 1·06, 95% CI 0·84 to 1·33., p=0·62), fetal deaths (0·89, 0·54 to 1·45., p=0·64), neonatal deaths (1·33, 0·54 to 3·28., p=0·53), and birth weight (–14 g,–100 to 126., p=0·81) did not differ between groups. No differences were found for any other secondary outcomes. Eight serious adverse events were reported during the course of the study (six in the placebo group and two in the sildenafil group). Interpretation., Sildenafil did not prolong pregnancy or improve pregnancy outcomes in severe early-onset fetal growth restriction and therefore it should not be prescribed for this indication outside of research studies with explicit participants' consent. In this study fetal growth restriction defined as a combination of estimated fetal weight or abdominal circumference below tenth percentile and absent or reversed end-diastolic blood flow in the umbilical artery on Doppler velocimetry which is exclusion criteria in our study

These findings were not consistent with ***Miller et al***. [26] who found in an experimental animal study that Sildenafil reduced uterine blood flow and this was associated with significant deterioration in fetal wellbeing. They explained their findings by the action of Sildenafil on maternal systemic circulation, altering it and resulting in blood flow "steal" from the uteroplacental circulation to the systemic vascular circulation that has lowered its resistance due to widespread systemic vasodilatation. They also provided an alternative explanation for the decrease in UBF which is the extensive cellular and tissue distribution of the PDE-5 enzyme throughout the body and therefore lack of relative specificity within the uteroplacental circulation. These findings of ***Miller et al.*** [26] in the animal study couldn't be confirmed in human.

Samangaya et al. [2] concluded that oral sildenafil in an escalating dose regime of 20–80 mg tid daily does not prolong pregnancy in women with preterm preeclampsia. The medication was well tolerated, and no women withdrew from the trial due to side effects. Up-titration to a maximal dose of 80mg tid was tolerated well by all women except one in the sildenafil group, who was down-titrated due to heartburn. Maternal adverse events occurred with a similar frequency in each group. Treatment had no effect on the condition of the babies at birth using Apgar scores at 1 and 5 minutes, and cord artery and vein pH samples. Most babies had at least one adverse event, with a similar incidence within each group. There was one neonatal death in the sildenafil group (extreme prematurity), and two in the placebo group (respiratory distress syndrome and a liver capsule tear). Although the sample size was small, the study was adequately powered to detect a difference of at least 5 days between treated and control groups in the time from randomization to delivery**.**

There are several explanations why this escalating regime of sildenafil did not affect outcome in women with preterm preeclampsia. Firstly, women may have been too far along the pathophysiological process, such that improving uteroplacental blood flow had no effect on release of circulating factors or on established endothelial dysfunction. Second the dosing regimen may not have achieved efficacious drug concentrations rapidly enough to slow progression, also within the study group there was a wide range of gestational ages, severity of preeclampsia and presence of fetal growth restriction. This reflects the heterogeneity of preeclampsia but may also have reduced the potential to demonstrate any effect of sildenafil [2].

Thus, from the obtained results, it is evident that sildenafil citrate treatment may offer a new opportunity to improve perinatal out comes for women whose pregnancies are complicated by IUGR.

CONCLUSION

To achieve optimal fetal growth, adequate blood flow in utero- placental vascular function is essential. Many authors have implicated abnormal vasculature adaptation, resulting in aberrant blood flow, as a possible cause of fetal growth restriction (FGR). Sildenafil citrate, as a vasodilator has also emerged as a potential management option in the treatment of FGR by normalization of fetal Doppler velocimetric profile.

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