Original Research Article

Sildenafil citrate therapy in intrauterine growth restriction with oligohydramnios

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Abstract

Background: Several short term and long-term adverse sequelae are linked with foetal growth restriction. In this study, the efficacy of Sildenafil citrate in improving the uteroplacental flow in pregnancies with intrauterine growth restriction was assessed.**Objectives:1.**To evaluate whether there is increase in uteroplacental blood flow in IUGR following sildenafil citrate therapy. **2.**To assess the potential benefits of sildenafil in IUGR, by serially measuring fetal abdominal circumference (AC) by ultrasonography**Materials & Methods:**Pregnant mothers in 24-33 weeks of gestational age having IUGR were randomized into two groups; Group A received 25 mg tablet of sildenafil citrate orally daily and Group B received no treatment. Maternal outcome like Gestational age at delivery and intervention to delivery interval (in days) were noted. Foetal outcomes like increase in foetal abdominal circumference (AC) by ultrasonography, change in pulsatilityindex in umbilical artery and change in Amniotic Fluid Index and birth weight were noted. **Results:**Mean birth weight with Sildenafil treatment was 2185 gram versus 2050 gram in the control group. AC growth velocity showed significant increase in mothers with sildenafil therapy (p 0.013). There was statistically significant decrease in pulsatility index value in umbilical artery in sildenafil treated group within 48 hours indicates increase in diastolic blood flow.**Conclusion:** Sildenafil treatment in IUGR showed trend in increase in birth weight of babies with increase in AC growth velocity, increasing trend in AFI with improved Doppler velocimetry, thus have a promising role in the management of IUGR.

Keywords: Sildenafil, IUGR, uteroplacental blood flow

Introduction

Human foetal growth is characterized by sequential pattern of tissue and organ growth, differentiation and maturation. Foetal development is determined by maternal provision of substrate and placental transfer of these. In human placenta foetal growth correlates with peroxisome proliferator activator receptor gamma (PPAR-γ) activity which governs placental regulation of L-type amino acid (LAT) receptors 1 and 2.[1]Intrauterine growth retardation (IUGR) is defined as a rate of growth of a foetus that is less than normal for the growth potential of a foetus (for that particular gestational age).To be more specific, IUGR is a foetal weight below tenth percentile for gestational age as determined by ultrasound.[2]Severe IUGR is referred to those babies whose birth weight is <3 percentile. Foetal growth restriction is one of the major obstetrical syndromes associated with defects in early placentation .[3] Several short term and long-term adverse sequelae are linked with foetal growth restriction.Incidence of IUGR varies between 10-15% among pregnancies without any medical comorbidities.[4]A lag in fundal height of 4 cm or more suggests IUGR. Serial ultrasonography at intervals of two to three weeks is considered as gold standard to detect IUGR. Foetal parameters that are monitored by ultrasonography include biparietal diameter, foetal head circumference, abdominal circumference and femur length. Among these, abdominal circumference is the most sensitive indicator. [5,6] Abdominal circumference (AC) measurements of less than 2 standard deviations below the mean may be a reasonable cut-off to consider a foetus asymmetric growth restriction.[7]Another important parameter estimated by ultrasonography is amniotic fluid index. Decreased volume of amniotic fluid is closely associated with IUGR. Uterine artery Doppler velocimetry is also important to identify foetuses at risk of IUGR. Sufficient uteroplacental blood flow is essential for normal pregnancy outcome.Some pregnancies with foetal growth restriction have elevated peripheral maternal vascular resistance in uterine arteries and hence poor perinatal outcome. Such pregnancies, if resistance values are normalized in later trimesters have a significantly better outcome.[8]Sildenafil citrate is a selective inhibitor of the type V cyclic guanosine monophosphate specific phosphodiesterase. Sildenafil enhances the effect of nitric oxide by inhibiting phosphodiesterase type 5, which is responsible for degradation of cyclic guanosine monophosphate. With the use of Sildenafil, cyclic guanosine monophosphate levels remain elevated which leads to endothelial dependent arterial vasodilatation in pregnancies complicated by IUGR.[9]Bed rest, protein supplementation, Fructodex, L-arginine, plasma volume expansion and low dose aspirin have been tried in the prevention and management of IUGR, but all have been proved not beneficial. Sildenafil, by virtue of vasodilator effect and increased placental flow may have a promising role in the management of foetal growth restriction. In this study, the efficacy of Sildenafil citrate in improving the uteroplacental flow in pregnancies complicated by intrauterine growth restriction was compared to a treatment-naïve control group by comparing the pregnancy outcomes.

Aims and objectives:

1. To assess the potential benefits of sildenafil in IUGR, by serially measuring fetal abdominal circumference (AC) by ultrasonography
2. To evaluate whether there is increase in uteroplacental blood flow in IUGR following sildenafil citrate therapy.

Material and methods

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Pregnant mothers of age 18-40 years in 24-33 weeks of gestation attending the antenatal outdoor of a tertiary care hospital were included in this study. Approved for the study was obtained fromInstitutional ethics committee. Written informed consent was taken from all the patients.

Inclusion criteria:Pregnant mothers in 24-33 weeks of gestational age having IUGR (Ultrasound estimation of foetal AC <10th percentile and Amniotic fluid index <5th percentile).

Exclusion criteria:

- Maternal cardiovascular morbidity
- Diagnosed cases of fetal aneuploidy syndrome
- Congenital infection
- Usage of any vasodilator medication
- Smoking
- Diabetes
- Vascular diseases
- Connective tissue disorder
- Autoimmune disease
- If any plan to terminate pregnancy before term

After informed consent, the study participants were randomized into two groups; Group Areceived 25 mg tablet of sildenafil citrate orally daily and Group B received no treatment. The uteroplacental perfusion was measured using transabdominal ultrasound Doppler velocimetry studies after 48 hrs of sildenafil citrate ingestion. If uterine blood flow increased and if no serious side effects were detected, 25 mg of sildenafil citrate was continued daily, in an attempt to reach term or near term. The mothers were constantly followed up with weekly ultrasound to monitor if there were significant changes in terms of estimated foetal weight, amniotic fluid index, abdominal circumference and umbilical arterypulsatility index. Maternal outcome like Gestational age at delivery and intervention to delivery interval (in days) were noted. Foetal outcomes like Increase in foetal abdominal circumference (AC) by ultrasonography, change in pulsatility Index in umbilical artery and change in Amniotic Fluid Index were calculated.Parameters of perinatal outcomes were Live births and Neonatal survival to hospital discharge.

Sample size: In view of logistical limitations formal sample size calculation was not considered; however, 30 subjects per group were included. Data was summarized by routine descriptive statistics. Numerical variables were compared between groups by Mann-Whitney U-test. Fisher's exact test was used for intergroup comparison of categorical variables. GraphPad Prism version 5 software [San Diego, California: GraphPad Software Inc., 2007] was used for the analysis. Variables were distributed by Kolmogorov-Smirnoff goodness-of-fit test.Mean was compared by using Student's unpaired t-test.

Results

Table 1: Baseline characteristics of Sildenafil treated (Group A) and Sildenafil naïve (Group B) cohorts.

Variables	Group A	Group B	P value
Age (Yrs)	25.6±0.48	24.8±0.56	0.28
BMI (Kg/m^2)	27.5±0.4	28.02±0.39	0.37
Parity –primi	20(66.67%)	18(60%)	0.789
Gestational Age at detection (weeks)	31.8±0.3	32.1±0.2	0.41
EFW (GMS)	1382.6±57.8	1508.4±53.4	0.11

In this case control study, 60 patients who have attended the antenatal clinic with features of IUGR, were included. They were randomized into Group A(Sildenafil treated) and Group B (Sildenafil naïve). Only the mothers whose foetus-in –utero showed growth defect with foetal AC<10th percentile for gestational age or amniotic fluid index <5th percentile in ultrasound, were included. The mean age for Group A and Group B are 25.6 years and 24.8 years respectively that is statistically insignificant (p value 0.28). Most of the patients in both groups are between 24-29 years. Similarly, BMI, Parity and mean gestational age at the time of recruitment were comparable and statistically insignificant (Table1) The men estimated foetal weight in both groups were 1382.6 and 1508.4 grams respectively at the time of recruitment and they were statistically comparable (p 0.11)

Table 2: Distribution of outcome in two groups according to foetal outcome

Variables	Group A	Group B	P-Value
Gestational age at delivery (weeks)	36.5±0.1	36.1±0.1	0.11
Birth wt (gms)	2185± 59.23	2050 ± 41.26	0.065
AC growth velocity	0.1±0.011	0.07± 0.008	0.013
AFI change (within 2 weeks of recruitment cm/wk)	0.03± 0.011	-0.09± 0.038	0.000
PI change (within 48 hrs)	-0.01±0.001	0.00± 0.001	0.000

Table 2 shows that there is slight increase in mean gestational age of 36.5 weeks at the time of delivery, compared to 36.1 weeks in the control group, though that is not statistically significant (p 0.11) There is a trend in an increase of birth weight with Sildenafil treatment with mean birth weight of 2185 gram versus 2050 gram in the control group. Most promising part of the result is AC growth velocity which shows significant increase in mothers with sildenafil therapy(p 0.013). Regarding amniotic fluid, there is a trend in increase in amniotic fluid index in sildenafil treated group after two weeks compared to sildenafil naïve which showed slight decrease in AFI and the result is statistically significant.Decrease in pulsatility index value in umbilical artery in sildenafil treated group within 48 hrs indicates increase in diastolic blood flow and is statistically significant.

Discussion

In this case control study, 60 patients who have attended the antenatal clinic with features of IUGR, were included. Only the mothers whose foetus-in –utero showed growth defect with foetal AC<10th percentile for gestational age or amniotic fluid index <5th percentile in ultrasound, were included. The mean age for Group A and Group B are 25.6 years and 24.8 years. Most of the patients in both groups are between 24-29 years. Regarding the effect of age on IUGR, there is conflicting reports. According to the study done by P von Dadelszen et al[10],the mean age of the patients were 33 years.Odibo et al[11] showed that there was a positive association between increasing maternal age and increasing risk for IUGR. At maternal age of 40 years or older, the OR and 95% CI for IUGR was 3.2 and 1.9 to 5.4 respectively. Thus, advanced maternal age is an independent risk factor for IUGR. This study suggests that screening for IUGR is indicated in women age 35 years or older. However, another study by Eduardo Durans Figuerêdo [12]showed that there is no statistically significant association between maternal age and increased prevalence of intrauterine growth restriction. More number of IUGR incidence in earlier age group, in our study can be

explained by earlier mean age of antenatal mother compared to the western counter part.There was slight but statistically insignificant increase in gestational age with sildenafil treatment with mean gestational age for Group A and Group B are 36.5 weeks and 36.1 weeks respectively. There was a trend of increased birth weight: the mean birth weight in sildenafil treated group (Group A) was 2185.9 gms and in Group B was 2050 gms(p value 0.065).Study by Pellicer B et alshowed sildenafil citrate increases foetal weight gain.[13] Another study by Ramesar SV et al[14] showed that sildenafil citrate decreases foetal mortality and demonstrated a trend toward increasing birth and placental weights in pregnant, L-NAME treated, Sprague-Dawley rats. A study by Herraize et al[15]showed sildenafil citrate improves perinatal outcome in foetuses from pre-eclamptic rats. Satterfield et al showed sildenafil citrate treatment enhances amino acid availability in the conceptus and foetal growth in an ovine model of intrauterine growth restriction.[16] They also showed that sildenafil citrate treatment dose-dependently increased foetal weight (P<0.05) in both nutrient-restricted and adequately fed ewes.This study supports the hypothesis that long-term sildenafil citrate treatment enhances foetal growth by increasing the availability of amino acids in the conceptus.In Group A the mean growth in AC velocity is 1.0 compared to 0.07 in Group B (p value 0.013) which is again statistically significant. According to the study done by P von Dadelszen et al[10] sildenafil treatment was associated with increased foetal AC growth velocity with odds ratio 12.9.In Group A mothers a trend in increase in AFI was seen after two weeks of sildenafil therapy the mean value being 0.03±0.011 (cm/wk) indicating that sildenafil has a role in increasing AFI and hence improving foetal outcome. On the contrary there was a trend in decrease of AFI in sildenafil naïve group (mean -0.09±0.038). The p value comes around 0.000 which is statistically significant. Study by Joshi P et al[17] showed improvement of amniotic fluid status among 80% patients with IUGR and oligohydramnios by treatment with sildenafil, similar to the study by Maher MA et al[18]Group A again showed a trend in decrease in pulsatility index in umbilical artery in 48 hrs, the mean value being (-0.01±0.001).It indicates increase in diastolic flow in the uteroplacental circulation hence improving the foetal outcome. On the contrary, Group B showed practically no change in PI over 48 hrs, the mean being (0.00±0.001). The p value is 0.000 which is statistically significant.Lin et al[19] also showed 2 weeks of sildenafil citrate treatment at 28 weeks gestation improves the uterine artery pulsatility index.MarziehVahid Dastjerdi et al[20] study showed that sildenafil group foetuses demonstrated a significant decrease in systolic/diastolic ratios (P=0.000), and a pulsatility index (P=0.019) for umbilical artery and a significant increase in middle cerebral artery pulsatility index (P=0.008).

There was safety concern regarding maternal side effects and also foetal effect due to placental transfer.SamangayaRA et al[21] have shown that sildenafil crosses the placenta. However systematic review by Villanueva-Garcia D et al[22] had commented that sildenafil is not a teratogenic agent. In this study, no significant adverse effects were seen with 25 mg sildenafil.

Conclusion

Till date there is no effective dug or treatment to improve feto-maternal outcome in pregnancies complicated with IUGR. The diagnostic evaluation has shown improvement with the application of Doppler studies, thus making the diagnosis much earlier. Similarly, advancement has been recognized in the pathophysiology of IUGR in the form of decreased perfusion in the uteroplacental bed. All these advances have led to emergence of several clinical trials especially with drugs like sildenafil which is a potent vasodilator.In this study sildenafil treatment in IUGR showed trend in increase in birth weight of babies with increase in AC growth velocity which was statistically significant. There was increasing trend in AFI with improved Doppler velocimetry in the form of decreasing PI in umbilical artery which suggests vasodilatation and increased diastolic flow.

Limitations: Study subjects were small in number. The study was done in very short period of time therefore long-term outcome of both mothers and new-born were not included.

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