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ORIGINAL ARTICLE

A Comparative Study to assess the Efficacy of Sildenafil Citrate and L-arginine in the Management of Fetal Growth Restriction

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ABSTRACT

Objective: To evaluate the efficacy of sildenafil citrate and L-arginine in the pregnancies complicated with fetal growth restriction (FGR) in terms of improvement in color Doppler parameters and perinatal outcome.

Materials and methods: In this study, we included 218 antenatal patients with FGR. After randomization, 110 women received sildenafil and 108 women L-arginine. Various fetal color Doppler parameters of umbilical artery (UA) and middle cerebral artery (MCA) were studied and followed until delivery, and perinatal outcome was evaluated.

Results: There was significant improvement in mean pulsatility index (PI) of the UA and MCA ($p < 0.05$). The systolic/diastolic (S/D) ratio and cerebroplacental ratio (CPR) also improved to a significant level. Perinatal outcome appears better in sildenafil group as compared with the L-arginine group.

Conclusion: Sildenafil citrate, as a vasodilator, has emerged as a potential management option in the treatment of FGR by later normalization in velocimetric profile.

Keywords: Cerebroplacental ratio, Fetal growth restriction (FGR), L-arginine, Middle cerebral artery (MCA), Pulsatility index (PI), Sildenafil citrate, Umbilical artery.

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INTRODUCTION

Fetal growth restriction (FGR) is defined as the estimated fetal weight below the 10th percentile for their gestational age. Its incidence is 3 to 10% of all births, and perinatal mortality increases 4 to 8 times for a growth-retarded infant. Fetal growth restriction is the second common cause of perinatal morbidity.[1]

In normal pregnant woman, nitrous oxide (NO) plays an important role in increasing the oxygen and nutrient supply to the fetus by influencing vasodilatation in the feto-placental circulation. Reduced NO availability may have an important role in the pathophysiology of FGR.[2] The NO donors (glyceryl trinitrate and isosorbide mononitrate), precursor (L-arginine), and NO mediator (sildenafil citrate and vardenafil) may be possible therapeutic approaches for FGR. In these NO agents, L-arginine or sildenafil citrate supplementation in pregnancy has recently been applied to manage FGR and its complications in many clinical studies.

Sildenafil citrate is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase-5 and enhances the effect of NO. It acts by blocking the enzyme that breaksdown cGMP, which mediates the effects of NO in the body and leads to vascular relaxation.

L-Arginine is an essential amino acid, physiologically active in the L-form, which is synthesized by endothelial cells. It is a 2-amino 5-guanidine pentanoic acid (alpha-amino acid). It plays a significant role in fetal growth by stimulating insulin secretion and a precursor for both polyamine synthesis and nitric acid synthesis and leads to increased vascular relaxation in utero-placental circulation.

Color Doppler ultrasound (USG) provides valuable information about the hemodynamic condition of fetus and is an excellent modality to assess fetal jeopardy that helps in management of various high-risk pregnancies.

In this study, we evaluated the efficacy of sildenafil citrate and L-arginine in terms of improvement in color Doppler parameters and perinatal outcome in pregnancies complicated with FGR.

MATERIALS AND METHODS

The study was carried out in the Department of Obstetrics and Gynecology in collaboration with the Department of Radiodiagnosis in Sarojini Naidu Medical College, Agra, Uttar Pradesh, India.

Inclusion Criteria

Women with singleton pregnancy with gestational age between 27 and 34 weeks, with FGR suspected clinically and confirmed by USG, and having fetal weight below 10 percentile for their gestational age.

Exclusion Criteria

Congenital anomalies in fetus, women with heart disease, chronic hypertension before pregnancy, medical illness like thyroid disease, diabetes, tuberculosis, epilepsy and asthma, multiple pregnancies, users of any vasodilator agents, and severe oligohydramnios.

The study design was approved by the ethics committee of the institute.

A written informed consent was obtained from all subjects. In this study, we recruited 240 antenatal women with FGR over the period from July 2014 to January 2017. All the women were randomly divided into either sildenafil group or arginine group. Out of 240 antenatal women, 22 women were lost to follow-up. Of the remaining 218 women, 110 were in the sildenafil group and 108 were in the arginine group. Sildenafil group received sildenafil citrate 25 mg three times a day until delivery. The arginine group received L-arginine 3 gm twice a day until delivery.

After taking a thorough clinical history, detailed general, systemic, and obstetrical examinations were done at the first visit, and then after 2 weeks with administration of sildenafil and L-arginine.

Ultrasonographic biometry, fetal weight, amount of liquor, and placental localization was done. Pulsed-wave Doppler velocimetry measurements were performed with color flow Doppler guidance on the umbilical and MCAs with an angle of insonation of <30°, before and after the treatment. Vascular flow velocity investigation was carried out by means of color Doppler imaging system equipped with a 3.5 to 5 MHz convex transducer and a 100 Hz high-pass filter. The S/D, resistance index (RI), and PI for the middle cerebral, uterine, and UAs were obtained by averaging the value of three consecutive waveforms.

Cerebroplacental Ratio

The MCA/UA PI ratio, which measures the proportion of bloodflow supplying the brain and placenta, was also measured. Single cutoff value <1.00 has high specificity and positive predictive value for FGR. Color Doppler was repeated after every 2 weeks until delivery to assess the outcomes as:

Primary outcome was in terms of improvement in Doppler indices that were PI in UA and MCA, S/D ratio in UA, CPR = PI of MCA/PI of UA.

Secondary outcome was in terms of mode of delivery, birth weight, APGAR score, admission to neonatal intensive care unit (NICU).

Statistical Analysis

The data were entered in MS Excel and standard statistical techniques were applied according to suitability of data. Significances of differences in outcome variables between groups were tested by unpaired t-test and Chi-squared test. The p-value < 0.05 was considered statistically significant with 95% confidence interval.

RESULTS

The mean gestational age in sildenafil group was 31.36 ± 2.6 weeks and in arginine group, it was 32.10 ± 2.4 week. Only 37.3% women in sildenafil group and 39.8% in arginine group had discrepancy in symphysiofundal height of more than 4 cm. Abdominal girth is measured after 30 weeks; so, out of 52 women in sildenafil group, 90.39% and out of 48 women in arginine group, 85.42% had more than two inches difference in abdominal girth. After excluding the women with severe oligohydramnios, 60.9% women in sildenafil group and 54.6% in arginine group had mild-to-moderate oligohydramnios. Mean amniotic fluid index in sildenafil group was 9.8 ± 2.4 and in arginine group was 9.9 ± 2.7. Increase in mean fetal weight at various gestational ages in women receiving sildenafil citrate is demonstrated in Table 1 and in women receiving L-arginine in Table 2.

The mean UA PI in sildenafil group at various gestational ages at follow-up showed gradual decrease, which was statistically significant (Graph 1).This difference was even more in that group of women in whom it was started at early gestation age. In arginine group, the PI of UA showed statistically significant decrease even in women in whom treatment was started at 33 weeks of gestation (Graph 2).

The mean MCA PI at various gestational ages during follow-up in the sildenafil and arginine groups showed gradual decrease, which was statistically significant after 2 to 4 weeks of treatment. Difference was highly significant ($p < 0.001$) in the sildenafil group as compared with the arginine group.

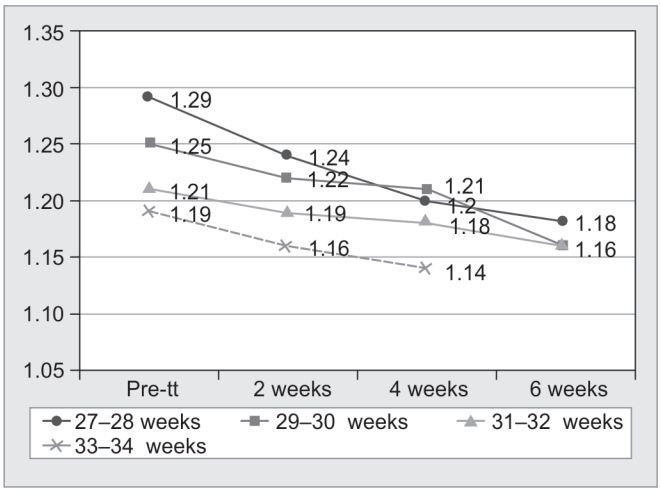
The S/D ratio of UA shows fall in both groups, which is represented in Graphs 3 and 4, which was statistically significant.

Table 1: Distribution of cases according to mean fetal weight (gm) at various gestational ages (sildenafil group)

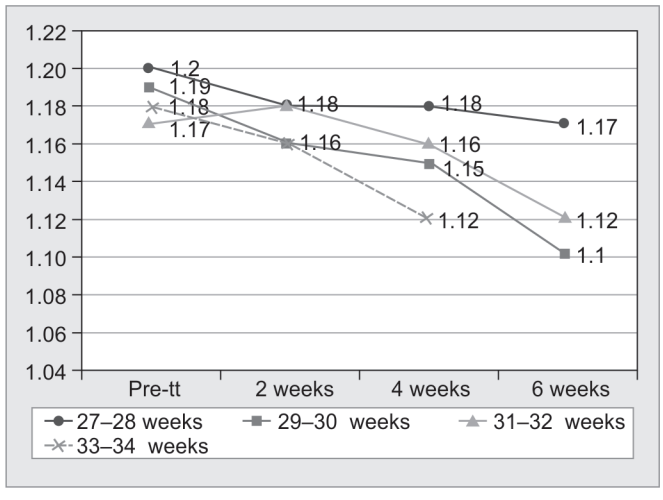
Gestational age (weeks)	*No of patients*	*Pretreatment*	*After 2 weeks*	*After 4 weeks*	*After 6 weeks*
27–28	30	721 ± 103.4	906.4 ± 207.4 p = 0.0001 t = 4.4	1.276.5 ± 307.6 p = 0.0001 t = 9.3	1.745.6 ± 325.6 p = 0.0001 t = 16.14
29–30	28	921.3 ± 209.2	1.196.6 ± 303.6 p = 0.0003 t = 3.87	1.496.6 ± 308.6. p = 0.0001 t = 7.62	1.995.4 ± 406.4 p = 0.0001 t = 10.82
31–32	34	1.104 ± 313.4	1.425.6 ± 416.6 p = 0.001 t = 3.444	1.975.7 ± 475.4 p = 0.0001 t = 8.3	2.476.7 ± 425.6 p = 0.0001 t = 10.82
33–34	18	1.409.6 ± 506.4	1.995.6 ± 505.6 p = 0.0006 t = 2.93	2.426.6 ± 425.6 p = 0.0006 t = 4.73	–

Table 2: Distribution of cases according to mean fetal weight (gm) at various gestational ages (arginine group)

Gestational age (weeks)	*No of patients*	*Pretreatment*	*After 2 weeks*	*After 4 weeks*	*After 6 weeks*
27–28	32	795.6 ± 203.4	845.6 ± 206.6 p = 0.12 t = 1.5	1,175.5 ± 405.7 p = 0.002 t = 4.2	1,695.5 ± 315.6 p = 0.0001 t = 10.32
29–30	28	905.6 ± 245.5	1,145.5 ± 215.5 p = 0.004 t = 3.74	1,445.6 ± 306.8 p = 0.0001 t = 6.60	1,895.5 ± 4.25 p = 0.0001 t = 8.93
31–32	30	1,110.6 ± 315.4	1,405.5 ± 405.5 p = 0.0002 t = 3.96	1,955.8 ± 455.4 p = 0.0001 t = 7.68	2,325.5 ± 450 p = 0.0001 t = 9.16
33–34	18	1,395.6 ± 402.5	1,875.7 ± 475.5 p = 0.002 t = 3.20	2,326.5 ± 450 p = 0.0001 t = 5.45	–

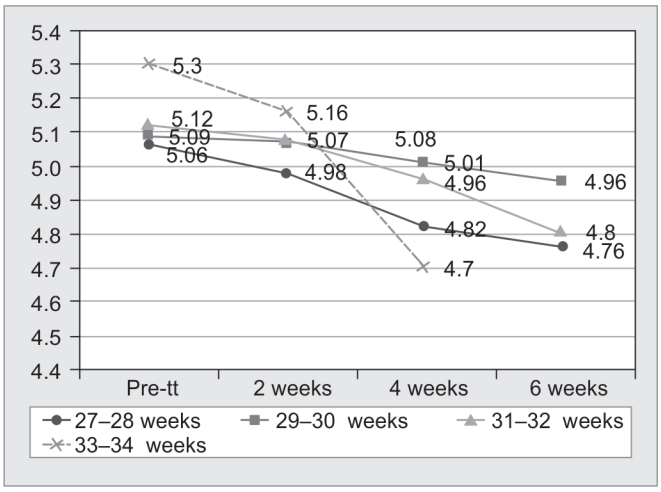


Graph 1: Distribution of cases according to mean UA PI (sildenafil group)

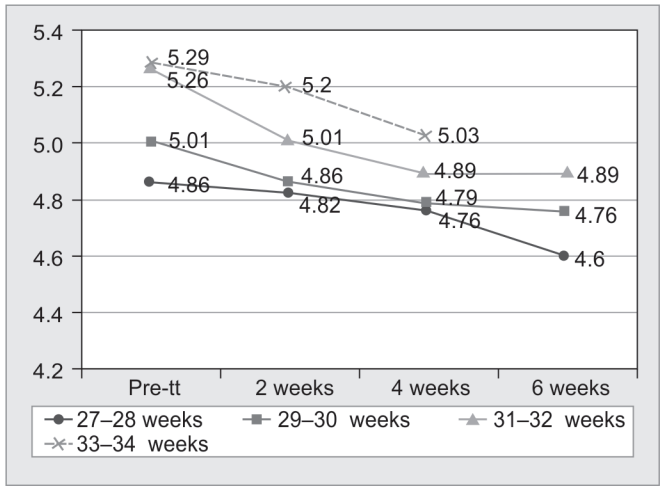


Graph 2: Distribution of cases according to mean PI of UA (arginine group)

The CPR in women treated with sildenafil citrate (Table 3) depicted a gradual increase. Mean CPR increased after treatment, which was statistically significant in the women with early gestation $p < 0.05$. Mean CPR at 27 to 28 weeks of gestation was 1.06 ± 0.16 before treatment and 1.17 ± 0.12 after treatment. Mean CPR was 1.06 ± 0.15 at 33 to 34 weeks of gestation before treatment and became 1.06 ± 0.15 after treatment. Thus, it shows no significant difference when it was given at a later gestational age. The CPR is a highly sensitive indicator of measurement of fetal hypoxia. In the arginine group, the mean value of CPR at 27 to 28 weeks before treatment was 1.18 ± 0.14, while after treatment it was 1.19 ± 0.12. At 33 to 34 weeks gestation, it was 1.08 ± 0.14



Graph 3: Distribution of cases according to UA mean S/D ratio (sildenafil group)



Graph 4: Distribution of cases according to UA mean S/D ratio (arginine group)

Table 3: Distribution of cases according to mean CPR middle cerebral artery pulsatility index/uterine artery pulsatility index (sildenafil group)

Gestational age (weeks)	*No of patients*	*Pretreatment*	*After 2 weeks*	*After 4 weeks*	*After 6 weeks*
27–28	30	1.06 ± 0.16	1.13 ± 0.14	1.15 ± 0.12	1.17 ± 0.12
			p = 0.07	p = 0.02	p = 0.01
			t = 1.80	t = 2.35	t = 2.6
29–30	28	1.08 ± 0.11	1.12 ± 0.12	1.14 ± 0.12	1.15 ± 0.16
			p = 0.20	p = 0.08	p = 0.14
			t = 1.27	t = 1.77	t = 1.48
31–32	34	1.11 ± 0.12	1.14 ± 0.13	1.15 ± 0.16	1.12 ± 0.14
			p = 0.34	p = 0.27	p = 0.79
			t = 0.96	t = 1.10	t = 0.26
33–34	18	1.06 ± 0.14	1.08 ± 0.14	1.06 ± 0.15	–
			p = 0.72	p = 1	
			t = 0.36	t = 0	

Table 4: Distribution of cases according to CPR middle cerebral artery pulsatility index/uterine artery pulsatility index (arginine group)

Gestational age (weeks)	*No of patients*	*Pretreatment (CPR)*	*After 2 weeks*	*After 4 weeks*	*After 6 weeks*
27–28	32	1.18 ± 0.14	1.16 ± 0.12	1.18 ± 0.14	1.19 ± 0.12
			p = 0.54	p = 1.0	p = 0.84
			t = 0.64	t = 0.00	t = 0.19
29–30	28	1.15 ± 0.12	1.17 ± 0.12	1.15 ± 0.12	1.17 ± 0.11
			p = 0.54	p = 1.0	p = 0.647
			t = 0.60	t = 0.00	t = 0.46
31–32	30	1.08 ± 0.12	1.10 ± 0.14	1.14 ± 0.11	1.12 ± 0.11
			p = 0.57	p = 0.08	p = 0.37
			t = 0.57	t = 1.76	t = 0.89
33–34	18	1.08 ± 0.14	1.09 ± 0.09	1.10 ± 0.11	–
			p = 0.8	p = 0.70	
			t = 0.25	t = 0.34	

t = unpaired t-test

before treatment and 1.10 ± 0.11 after treatment (Table 4) ($p > 0.05$).

Perinatal outcome was assessed in terms of mode of delivery, APGAR score at 1 and 5 minutes, and NICU admissions. Table 5 shows the distribution of both groups according to their perinatal outcome. However, the odds ratio = 0.5 indicated that in the sildenafil group there is 50% less chances of NICU admission as compare with the L-arginine group.

DISCUSSION

This study investigated the effect of sildenafil citrate and L-arginine on uteroplacental perfusion and it appears that introduction of these preparations at an early gestational

Table 5: Distribution of cases according to mode of delivery and neonatal outcome in both groups

	Sildenafil group		*Arginine group*	
Mode of delivery				
Vaginal	46 (41.81%)		35 (32.40%)	
Cesarean	64 (58.18%)		73 (67.59%)	
Neonatal outcome				
Mean birth weight	2,880 ± 240.5		2,680 ± 310.6	
APGAR score	At 1 min	At 5 min	At 1 min	At 5 min
<7	34	21	36	29
≥7	76	89	72	79
NICU admission				
Yes	26	23.63%	36	33.33%
No	84	76.36%	72	66.66%

age was associated with significant changes in the fetoplacental Doppler flow velocimetry.

In the present study, mean UA PI shows gradual fall after treatment in both groups, which was statistically significant (p = 0.0001). This finding is consistent with Dastjerdi et al.,[3] who demonstrated a decrease in mean UA PI in the sildenafil-treated group as compared with the sildenafil-naïve group. In their study, the mean UA PI in the sildenafil-treated group was 1.13 ± 0.10, which decreased to 1.01 ± 0.13 after treatment. This difference was significant statistically (0.019) as compared with that of the control group (1.04 ± 0.35 *vs* 1.02 ± 0.31; p = 0.60). Singh et al[4] demonstrated that uterine artery PI showed a good diagnostic efficacy with an accuracy of 79%, a sensitivity of 76.9%, and specificity of 82.9%. Both PI and RI for uterine artery showed a relatively higher specificity. Our study shows increase in mean PI of MCA with sildenafil treatment, but it was statistically more significant when introduced at early gestation (27–28 weeks p = 0.0001). Dastjerdi et al[3] studied MCA PI and demonstrated significant increase in mean MCA PI (1.07 ± 0.04 *vs*. 2.18 ± 0.65) in the study group with p = 0.008.

There was a significant fall in UA S/D ratio (p = 0.0001) with sildenafil and arginine. In a study by Dastjerdi et al.,[3] the mean S/D ratio in UA before and after sildenafil treatment was 3.26 ± 0.54 and 2.66 ± 0.33 respectively, and this difference was significant (p = 0.000), but not in the other group, which received only placebo (p = 0.22). Singh et al[5] studied the role of arginine in FGR and suggested that IUGR pregnancies with S/D ratio less than 4.96 ± 0.49 and NO levels below 33 µmol/L were the ideal candidates for arginine therapy, and that with minimum of 3 weeks duration of arginine supplementation showed significant improvement.

In the present study, there was a significant increase in CPR in the sildenafil group in early gestation (p = 0.01) and no significant increase in CPR in L-Arginine group (p = 0.70). Kant et al[6] showed that CPR specificity and positive predictive value were 100%; however, specificity was 22.9% and negative predictive value was 56.5%.

Mean birth weight improved in our study, which is consistent with Dastjerdi et al.,[3] which showed birth weight was significantly lower in patients with persistently abnormal velocimetry profile *vs* those with normal velocimetry at 24 weeks or those with later normalization.

In the Baschat et al[7] study, the rate of cesarean delivery was 97.1% in the fetal growth restricted group in comparison with the 69.6% women in the group that did not receive sildenafil, which is consistent with our study, wherein it was 58.18 and 67.59% in sildenafil and arginine groups respectively.

Although there is no study on its placental transfer, sildenafil has a relatively low molecular weight and might cross the placenta and exert a direct effect on fetoplacental circulation as a mild NO donor in the peripheral vasculature. Common side effects of sildenafil that are described in the literature like headache, flushing, dyspepsia, nasal congestion, and diarrhea were observed in few women, but it is a quite well-tolerated drug.

CONCLUSION

Our study shows that sildenafil is as effective as L-arginine in the management of FGR. Sildenafil shows significant improvement in color Doppler indices and also showed improvement in mean fetal weight. The APGAR score was improved along with less NICU admission rates in the sildenafil-treated group.

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