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Difference between Oral Isosorbide Mononitrate & Sildenafil Citrate Therapy in Reducing Umbilical Artery Doppler Indices in Pregnancies with Fetal Growth Restriction; A Prospective Randomized Control Trial

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ABSTRACT

Background: Fetal growth restriction (FGR) occurs when a fetus does not attain its genetically assigned expected growth rate. An estimated fetal weight (EFW) or abdominal circumference (AC) below the 10th percentile for gestational age is the ideal definition of this condition.

Objectives: This study aimed to compare isosorbide mononitrate and sildenafil citrate therapies in the context of pregnancies complicated by FGR regarding the magnitude of reduction in umbilical artery (UA) Doppler resistance index (RI) in a randomized fashion.

Patients and Methods: This research was carried out in the Maternity Hospital of Ain Shams University during the period from March to September 2020. 64 pregnant women with FGR, were recruited from the antenatal clinic. They were subdivided into 2 groups according to a randomization table (Isosorbide mononitrate group versus sildenafil citrate group).

Results: The administration of isosorbide mononitrate 30 mg twice daily is as effective as sildenafil citrate 50 mg twice daily in reducing umbilical artery Doppler resistance index (RI), thereby enhancing fetal growth in pregnancies with FGR and in turn reducing the overall perinatal morbidity and mortality caused by iatrogenic prematurity or FGR itself.

Conclusion: We recommend the use of isosorbide mononitrate as a therapeutic agent in pregnancies with FGR caused by placental insufficiency.

Keywords: FGR, Doppler ultrasound, Isosorbide mononitrate, Sildenafil citrate.

INTRODUCTION

Fetal growth restriction (FGR) occurs when a fetus is unable to reach its genetically set potential size. It is defined as an estimated fetal weight (EFW) or abdominal circumference (AC) below the 10th percentile for gestational age [(1)].

Increased perinatal mortality and morbidities, including hypothermia, hypoglycemia, neonatal jaundice, respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), and sepsis, are all likely consequences of iatrogenic prematurity in growth-restricted fetuses with significantly reduced umbilical artery (UA) blood flow [(2)].

In a physiological pregnancy, nitric oxide (NO), a strong vasodilator that also suppresses platelet aggregation, is secreted by the placental trophoblast. It was found that placental ischemia and endothelial dysfunction are linked to reduced NO production and enhanced phosphodiesterase type 5 (PDE-5) activity in FGR-affected pregnancies. As a result, isosorbide mononitrate (NO donor) and sildenafil citrate (PDE-5 inhibitor) may be used to both prevent and treat FGR [(3)].

Isosorbide mononitrate, as a nitric oxide (NO) donor, can induce vasodilation in the fetoplacental circulation, in order to promote nutrient and oxygen supply to the fetus, via its direct effects on smooth muscle. Through its impact on guanylate cyclase (GC), which is a precursor of cyclic guanosine monophosphate (cGMP). NO enhances the production of cGMP, which then stimulates protein kinase G that in turn activates myosin phosphatase causing calcium to be released from its intracellular stores. Therefore, it helps to regulate fetoplacental perfusion by counteracting the action of other vasoconstrictive substances [(4)]. Isosorbide mononitrate and other nitrates are powerful vasodilators. They cause venodilation at relatively low doses. They do, however, cause arterial vasodilatation at low to moderate doses. The degree of sympathetic reflex discharge, the dose given, and the presence or lack of nitrate tolerance all influence the overall hemodynamic response to nitrate [(5)].

MATERIALS AND METHODS

This research study was carried out at Maternity Hospital of Ain Shams University during the period from March to September 2020. It included 64 pregnant women with FGR recruited from the antenatal clinic. They were randomised into two groups using a randomization procedure.

Inclusion criteria: Patients with a singleton intrauterine pregnancy complicated by FGR (EFW<10th percentile for GA) whose age ranges from 18-35 years

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old, BMI 20-30 Kg/m^2 and with gestational age ranging from 28 to 34 weeks.

Exclusion criteria

Patients with pre-pregnancy medical disorders as DM, hypertension, pregnancy-induced medical disorders as gestational DM, pre-eclampsia and eclampsia and known intolerance to isosorbide mononitrate or sildenafil. Patients taking nitroglycerine, sodium nitroprusside, alpha blockers and protease inhibitors. Patients with congenital fetal malformations (CFMF) or intra uterine fetal death (IUFD) and absent or reversed end-diastolic umbilical artery doppler velocity.

Ethical approval

This study has been approved by the Ethics Board of Ain Shams University. An informed written consent, including details, benefits and possible risks of the study, was taken from each participant. This work was undertaken in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data analysis was done with the use of IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY). Mean and SD were used to represent normally distributed numerical data, while median and interquartile range were used for skewed or discrete data. The unpaired t-test was utilized in between-group comparisons of normally distributed numerical data, while the paired t-test was applied in paired comparison of normally distributed numerical data. Comparison of independent skewed or discrete numerical data was performed using the Mann-Whitney test, while comparison of multiple within-group measures was done using repeated-measures analysis of variance (ANOVA). The p-value for multiple within group comparisons was adjusted using the Bonferroni correction the p-value with a statistically significant two-sided, p-value being equal or less than 0.05 (p-value $\leq$ 0.05).

RESULTS

There was no statistically significant difference in baseline patient characteristics, including age, weight, height, BMI, parity and gestational age, among both study groups as shown in table (1).

Table (1): Characteristics of patients in both study groups

- Number of previous abortions	1 (0 to 1)	1 (0 to 2)	.364§
- Gestational age (weeks)	31.8 ± 2.2	32.1 ± 1.8	.567 ¶

Variable	**Isosorbide Mononitrate *(n=32)***	**Sildenafil Citrate *(n=32)***	***p-value***
- Age (years)	27.8 ± 4.2	28.6 ± 4.1	.743¶
- Weight (kg)	69.7 ± 8.3	72.7 ± 8.6	.155¶
- Height (cm)	164.8 ± 5.3	165.9 ± 5.0	.371¶
- BMI (kg/m^2)	25.6 ± 1.7	26.4 ± 2.1	.112¶
- Number of previous deliveries	2 (1 to 3)	2 (0 to 3)	.598§

Data are mean ± SD or median (interquartile range). **¶ Unpaired t-test. §Mann-hitney test.**

In addition, the magnitude of reduction in systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) did not show any statistically significant difference between both study groups during the 1st and 3rd weeks of the study as shown in table (2); Similarly, there was no statistically significant difference in the magnitude of reduction in Umbilical artery Doppler resistance index (UA RI) as shown in table (3).

Table (2): Arterial BP in both study groups

Variable	*Time*	*sosorbide Mononitrate (n=32)*	*Sildenafil Citrate (n=32)*	*-value¶*
SBP (mmHg)	*Baseline*	118 ± 10	18 ± 10	.000
	Week 1	110 ± 9	12 ± 9	351
	Weeks 3	106 ± 8	08 ± 8	263
DBP (mmHg)	*Baseline*	76 ± 6	5 ± 6	378
	Week 1	73 ± 6	1 ± 6	326
	Weeks 3	69 ± 7	9 ± 6	325
MAP (mmHg)	*Baseline*	90 ± 6	9 ± 5	549
	Week 1	85 ± 6	5 ± 6	341
	Weeks 3	81 ± 7	2 ± 6	518

Data are mean ± SD. **¶ Unpaired t-test.**

Table (3): UA RI in both study groups

Variable	*Time*	*Isosorbide Mononitrate (n=32)*	*Sildenafil Citrate (n=32)*	*p-value¶*
UA RI	*Baseline*	0.80 ± 0.05	0.83 ± 0.05	.036
	Week 1	0.75 ± 0.06	0.77 ± 0.07	.213
	Weeks 3	0.71 ± 0.05	0.73 ± 0.05	.127

Data are mean ± SD. **¶ Unpaired t-test.**

Moreover, there was no statistically significant difference between both study groups as regards the magnitude of enhancement in estimated fetal weight (EFW) and fetal abdominal circumference (AC) over the period of the study (3 weeks), where fetal growth gain was 500 gm, in average, after receiving Isosorbide Mononitrate and Sildenafil Citrate respectively as shown in table (4).

Table (4): Fetal biometric measures in both study groups

Variable	*Time*	*sosorbide Mononitrate n=32)*	*ildenafil Citrate (n=32)*	*-value¶*
Estimated gestational age (weeks)	*Baseline*	8.7 ± 2.4	8.7 ± 1.9	967
	Weeks 3	3.2 ± 2.2	3.1 ± 1.9	389
Estimated fetal weight (g)	*Baseline*	034 ± 249	036 ± 244	976
	Weeks 3	541 ± 249	543 ± 256	980
AC (mm)	*Baseline*	17 ± 26	22 ± 29	509
	Weeks 3	55 ± 27	57 ± 31	760

Data are mean ± SD. **¶ Unpaired t-test.**

However, there was a statistically significant reduction in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and umbilical artery resistance index (UA RI) within each study group over the period of the study (3 weeks) as shown in tables (5) and (6).

Table (5): Percentage of change in arterial blood pressure and UA RI in both study groups

Variable	*Time*	*Isosorbide Mononitrate (n=32)*	*Sildenafil Citrate (n=32)*	*p-value¶*
% Change in SBP	*Week 1*	8.3 (-9.1 to -3.8)	7.7 (-8.3 to 0.0)	.049
	Week 3	9.1 (-9.1 to -8.3)	8.3 (-9.5 to 0.0)	.126
% Change in DBP	*Week 1*	.0 (-12.5 to 0.0)	6.3 (-12.5 to 0.0)	.660
	Week 3	14.3 (-16.7 to 0.0)	14.3 (-14.3 to 0.0)	.451
% Change in MAP	*Week 1*	4.0 (-8.3 to -3.6)	5.4 (-8.3 to -3.4)	.747
	Week 3	10.7 (-12.0 to -6.9)	8.3 (-11.3 to -3.8)	.203
% Change in UA RI	*Week 1*	6.1 (-7.9 to -3.7)	5.0 (-8.9 to -3.8)	.761
	Week 3	10.0 (-12.8 to -9.0)	10.8 (-13.9 to -8.6)	.686

Data are median (interquartile range). **¶ Mann-Whitney test.**

Table (6): Percentage of change in fetal biometric measures in both study groups

Variable	*Isosorbide Mononitrate (n=32)*	*Sildenafil Citrate (n=32)*	*p-value¶*
% Change in EGA	13.9 (12.8 to 15.0)	15.0 (13.0 to 15.7)	.277
% Change in EFW	47.5 (36.8 to 52.0)	48.5 (41.8 to 59.3)	.336
% Change in AC	14.7 (11.1 to 17.1)	15.4 (12.9 to 17.5)	.454

Data are median (interquartile range). **¶ Mann-Whitney test.**

Eventually, there was statistically significant enhancement in fetal biometric measures including estimated gestational age (EGA), estimated fetal weight (EFW) and fetal abdominal circumference (AC) within each study group over the period of the study (3 weeks) as shown in tables (7) and (8).

Table (7): Within-group comparison of blood pressure and UA RI

Variable	*Time*	*Isosorbide Mononitrate (n=32)*	*Sildenafil Citrate (n=32)*
SBP (mmHg)	*Baseline*	118 ± 10	118 ± 10
	Week 1	110 ± 9†	112 ± 9†
	Week 3	106 ± 8†‡	108 ± 8†‡
	p-value¶	<.001	<.001
DBP (mmHg)	*Baseline*	76 ± 6	75 ± 6
	Week 1	73 ± 6†	71 ± 6†
	Week 3	69 ± 7†‡	69 ± 6†‡
	p-value¶	<.001	<.001
MAP (mmHg)	*Baseline*	90 ± 6	89 ± 5
	Week 1	85 ± 6†	85 ± 6†
	Week 3	81 ± 7†‡	82 ± 6†‡
	p-value¶	<.001	<.001
UA RI	*Baseline*	0.80 ± 0.05	0.83 ±
	Week 1	0.75 ± 0.06†	0.77 ± 0.07†
	Week 3	0.71 ± 0.05†‡	0.73 ± 0.05‡

Data are mean ± SD. ¶ ANOVA. †Statistically significant difference vs. Baseline (Bonferroni-corrected p-value <.01). ‡Statistically significant difference vs. Week 1 (Bonferroni-corrected p-value <.01).

Table (8): Within-group comparison of fetal biometric measures

Variable	*Time*	*Isosorbide Mononitrate (n=32)*	*Sildenafil Citrate (n=32)*
Estimated gestational age (weeks)	*Baseline*	28.7 ± 2.4	28.7 ± 1.9
	Week 3	33.2 ± 2.2	33.1 ± 1.9
	p-value¶	<.0001	<.0001
Estimated fetal weight (g)	*Baseline*	1034 ± 249	1036 ± 244
	Week 3	1541 ± 249	1543 ± 256
	p-value¶	<.0001	<.0001
AC (mm)	*Baseline*	217 ± 26	222 ± 29
	Week 3	255 ± 27	257 ± 31
	p-value¶	<.0001	<.0001

Data are mean ± SD.
¶ Paired t-test.

DISCUSSION

Fetal growth restriction (FGR) is a leading cause of perinatal morbidity and mortality worldwide. Although precise fetal growth assessment during pregnancy is challenging, recent advances in ultrasound have enhanced this crucial component of obstetric care, with good implications for pregnant ladies and their neonates [(6)]. FGR refers to a fetus that has not reached a certain weight threshold (less than 10th percentile for gestational age). Intrinsic (genetic) and extrinsic (placental and maternal) variables influence fetal growth. Failure of any one of these factors, or a combination of them, will stunt the growth of affected fetuses. Because clinical care, counseling, and outcome of pregnancy are all linked to the etiology, determining the particular cause of FGR prior to delivery is crucial [(7)].

For ideal in-utero fetal growth, it is necessary to have sufficient blood flow in the fetoplacental circulation. FGR is assumed to be the outcome of aberrant vascular adaptation, which causes abnormal blood flow [(8)].

Sildenafil citrate, a PDE-5 inhibitor, and isosorbide mononitrate, a nitrate that have been proposed as vasodilators to be used as therapeutic agents in FGR-affected pregnancies by causing vasodilatation in myometrial small arteries, lowering peripheral arterial resistance, and enhancing utero-placental perfusion [(9)].

The goal of this study was to assess the effects of isosorbide mononitrate and sildenafil citrate on the resistance index (RI) of the umbilical artery (UA) and, as a result, on fetal growth pattern in FGR pregnancies, as well as to predict their perinatal prognosis.

The research was conducted at the Ain Shams University Maternity Hospital's Obstetric Outpatient Clinic. It involved 64 pregnant women with a singleton intrauterine pregnancy complicated by FGR who were divided into two groups:

- Group A (n=32): "Isosorbide mononitrate group" who received IMDUR 30 mg tablet twice daily.
- Group B (n=32): "Sildenafil citrate group" who received VIRECTA 50 mg tablet twice daily.

Comprehensive history was taken and thorough physical examination was done to all the participants. The umbilical artery (UA) resistance index (RI) was compared before and weekly after receiving isosorbide mononitrate and sildenafil citrate for three weeks in each group. At the end of the three weeks, ultrasound measurements EFW and AC were measured and compared to baseline values.

Our results showed a non-statistically significant difference in maternal characteristics such as age, BMI, parity, and number of previous abortions between the 2 groups. The mean age of our study participants was 27.8 years.

We found that there was a statistically significant reduction in umbilical artery resistance index (UARI) in both groups after initiating isosorbide mononitrate and sildenafil citrate therapy respectively, and both agents were almost equally effective.

At the end of the three weeks of the study, there was a statistically significant improvement in fetal biometric measures including estimated gestational age (EGA), EFW and AC, but no statistically significant difference between the efficacies of both study agents.

Dastjerdi *et al.* [10] found that patients with FGR-complicated pregnancies who received a single dosage of sildenafil citrate (50 mg) showed considerable improvement in umbilical artery Doppler indices 2 hours after receiving the medication, which is consistent with our findings. The current findings, which showed an improvement in utero-placental blood flow as evidenced by lower umbilical artery Doppler indices in FGR pregnancies after isosorbide and sildenafil administration, are supported by the findings of other case reports, such as **Panda *et al.* [8],** who found a decrease in UARI after ingestion of 50 mg sildenafil twice daily and increasing the dose of isosorbide. Sildenafil up to 50 mg three times daily in patients with FGR. **Choudhary *et al.* [11]** conducted a study that was similar to ours. After commencing vaginally administered sildenafil citrate 25 mg BID in a pregnant woman with abnormal umbilical artery Doppler, it exhibited an improvement in Doppler indices and an increase in baby's weight. **Sharp *et al.* [12]** also conducted a case-control study on pregnant women with FGR, finding a substantial increase in abdominal circumference (AC) in neonates who received sildenafil citrate 25 mg TID until birth. Sildenafil had no negative maternal side effects in this study.

Trapani *et al.* [2] performed a prospective study on patients with FGR and abnormal UA Doppler indices. The PI and RI of the umbilical artery decreased significantly following oral administration of 50 mg sildenafil citrate and transdermal application of a 50 mg transdermal GTN patch, however there were no statistically significant variation in the middle cerebral artery Doppler indices (RI and PI) in any of the study groups.

CONCLUSION

Our findings showed that giving isosorbide mononitrate 30 mg twice daily is as effective as giving sildenafil citrate 50 mg twice daily in improving umbilical artery Doppler indices over the course of three weeks. Thereby, they improved fetal growth in pregnancies with FGR and lowered the overall perinatal morbidity and mortality caused by iatrogenic prematurity or foetal growth restriction.

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