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Doppler Indices of Uterine, Umbilical and Fetal Middle Cerebral Arteries Before and After Sildenafil Citrate and Transdermal Nitroglycerin in Cases Suffering from Intrauterine Growth Restriction

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ABSTRACT

Introduction

Intrauterine growth restriction (IUGR) is a major cause of perinatal morbidity and mortality. Its diagnosis and treatment constitute one of the most important challenges of present day obstetrics. A drug that could improve maternal and fetal hemodynamics in the setting of early intrauterine growth restriction has potential benefit for at least palliation of this ominous condition. In most instances the etiology of IUGR is unknown. The absence of a uniform etiology may help one understand the existence of the large number of treatments suggested for correcting the problem

Patients and Methods

The objective of this study was to compare the effect of transdermal nitroglycerin and oral Sildenafil citrate on Doppler indices of uterine, umbilical and fetal middle cerebral arteries, and changes in fetal weigh, abdominal circumference and amniotic fluid volume in fifty pregnant women who attended inpatient and outpatient clinics in the department of Obstetrics & Gynecology in Tanta University Hospitals, and suffering from asymmetrical intrauterine growth restriction.

Results

of the study proved a clear significance of the growing role of transdermal nitroglycerin and Sildenafil citrate for augmenting, feto-placental blood flow in the setting of placental vascular insufficiency and IUGR, as a significant reduction in umbilical artery RI, uterine artery RI in the two groups, also abdominal circumference, AFI and estimated fetal weight were significantly increased after 21 days from treatment. That gives a promising treatment for IUGR patients.

INTRODUCTION

Intrauterine growth restriction (IUGR) is one of the most common complications of pregnancy and a major cause of prematurity. Growth-restricted fetuses with severe impairment of umbilical artery (UA) blood flow are at increased risk of adverse fetal outcomes such as intrauterine fetal demise, neonatal death, and neonatal morbidity; including hypoglycemia, hyperbilirubinemia, hypothermia, intraventricular hemorrhage, necrotizing enterocolitis, seizures, sepsis and respiratory distress syndrome.[1]

furthermore, epidemiological studies have shown that fetuses with IUGR are predisposed to delayed development in childhood ,and diseases in adulthood (e.g. obesity, Type II diabetes

mellitus, coronary artery disease and stroke).[2]

Drugs like nitric oxide and Sildenafil citrate increase the uterine blood flow. Studies have been done on them for their role in prevention and treatment of (IUGR).[3]

The nitric oxide (NO) is a potent venous and arterial vasodilator and platelet aggregation inhibitor, it is produced from the trophoblast and decreased in pregnancies complicated with pre-eclampsia or IUGR, so placental hypoxia and endothelial dysfunction are associated . It is an autocrine and paracrine signaling molecule that is synthesized from L-arginine by a family of calcium–calmodulin-dependent enzymes called nitric oxide synthases (NOS) . The organic nitrates include glyceryltrinitrate (GTN) or nitroglycerine and isosorbidedinitrate (ISDN). Glyceryltrinitrate (nitroglycerin, GTN) produces nitric oxide through a biotransformation. One of its limitations is the development of tolerance, which can be reduced with intermittent administration. Headache is one of the few reported side effects. [3,4,5]

Phosphodiesterase type 5 (PDE-5) is an enzyme that metabolizes cyclic guanosine monophosphate (cGMP). PDE-5 inhibition results in an increase in cGMP and consequent vasodilatation. Therefore, phosphodiesterase inhibitors have the potential to achieve similar therapeutic goals when compared with NO, but potentially without its side effect (i.e. tolerance and headaches). The most-studied PDE-5 inhibitor is sildenafil citrate, which has shown promising outcomes both in vitro and in animal studies.As studies showed that Sildenafil citrate increases uterine blood flow and potentiates estrogen-induced vasodilatation.[6,7]

The objective of this study is to compare the effect of-Sildenafil citrate and transdermal nitroglycerin on Doppler indices of uterine, umbilical and fetal middle cerebral arteries, and changes in abdominal circumference, fetal weigh and amniotic fluid index in patients suffering from asymmetrical intrauterine growth restriction.

PATIENTS AND METHODS

This prospective interventional follow up study had been conducted on (50) patients who attended inpatient and outpatient clinics in the department of Obstetrics & Gynecology in Tanta University Hospitals, for a period of at least 6 months. It is approved by Tanta University, Faculty of Medicine, Research ethics committee review, approval code; 31216/11/16.

Patients

Criteria of patient selection: Female patient aged between 20 to 35 years old, with singleton pregnancy ,gestational age between 24 to 33 weeks (gestational age has been calculated from the date of the last menstrual period or ultrasound examination performed during the first trimester of the pregnancy), body mass index "between" (22 to 30) , maternal Hb % > 11gm/dl, intact membranes, and with asymmetrical intrauterine growth restriction that resulted from placental insufficiency (diagnosed by U/S measures fetal abdominal circumference<5th percentile for gestational age, with normal head circumference and high Doppler resistance indices of umbilical and uterine arteries and normal fetal middle cerebral Doppler indices) as there is restriction of weight followed by length. The head continues to grow at normal or near-normal rates (head sparing). A lack of subcutaneous fat leads to a thin and small body out of proportion with the liver. Normally at birth the brain of the fetus is 3 times the weight of its liver. In IUGR, it becomes 5-6 times.[1,8] were included.

Symmetrical intrauterine growth restrictions due to fetal anomalies, chromosomal anomalies and congenital infection were excluded. Also usage of vasodilator agents, known contraindication for nitroglycerin or Sildenafil, reversed or absent umbilical artery diastolic flow, if prolongation of pregnancy will cause deterioration of the fetal or maternal conditions seriously ,and maternal diastolic blood pressure more than 110 mm Hg

Methods

All patients had been subjected to the following: • An informed consent had been obtained from all participants in this research.

- Full history taking
- General & local clinical examination.
- Fetal surveillance occurred at least as frequently as every 6–8 days for outpatients and at least twice weekly for inpatients, in the form of:

✓ Cardiotocography (CTG)
✓ Biophysical score (BPS)

The ultrasonographic examinations were performed with (Samsung UGEO H60. Korean manufacturer) to estimation of abdominal circumference, fetal weight, amniotic fluid index and Doppler indecies before receiving medications.

Convex abdominal transducer and a CD facility. The patients were asked to empty the urinary bladder just before the procedure, ultrasound coupling gel was applied to the probe and the patient was examined in the supine position.

Patients had been randomized into two groups :(A) sildenafil group (n=25) and (B) transdermal nitroglycerin group (n=25). Patients had been assigned to each treatment group based on blocked randomization with opaque envelop.

Sildenafil citrate had been administrated orally at a dose of 25 mg three times daily for 21 days (Silden 25 mg F.C. Tablets: Box containing a strip of 10 F.C. tablets, EpicoMan., Egypt).

A new 50-mg transdermal nitroglycerin patch (nitroderm TTS 10, NOVARTIS PHARMA S.A.E., under license from: Novartis Pharma AG., Basle, Switzerland), had been applied to the abdominal skin at 7:00 am or on awakening for sixteen hours per day for 21 days, women had been advised to change the site of application of transdermal nitroglycerin patches and warned about headache and slight skin erythema, Patients had been asked about the complications.

GTN and sildenafil citrate doses were selected based on the safety profile and favorable results from previous studies.[6,12,13,14]

Maternal blood pressure was measured, with the fourth Korotkoff sound used for determination of the diastolic blood pressure. mean arterial pressure (MAP) [((Diastole × 2) + Systole)/3], was used for calculation.

Ultrasound and Doppler measurements were always performed at 24 hours & 3 weeks after first sildenafil dose or nitro-Dermal patch application to avoid the impact of possible circadian variation in the parameters.

Resistance index (RI) (Peak systolic-End diastolic/Peak systolic velocity), and heart rate were measured from three consecutive and uniform waveforms in the uterine arteries, umbilical arteries, and fetal middle cerebral arteries. Both the left and right uterine arteries were visualized by color Doppler ultrasonography at the point at which they cross the iliac vessels, and the mean of the recordings of the right and left sides was used for calculation. Umbilical artery blood velocity waveform was recorded from a freely floating cord loop. The middle cerebral artery was identified by color Doppler ultrasonography in a transverse section of the fetal head and sampled slightly cranial to the thalamus. Umbilical and cerebral Doppler measurements were performed in the absence of fetal active body or breathing movements. Mean blood pressure (MBP) were calculated for the patients 24hours & 3 weeks after received the medication. Amniotic fluid index (AFI), Abd Circumference (Ac) and Estimated fetal weight (EFW) were measured for the patients in the two standard groups after 3 weeks from receiving the medication.

Potential Risks

Headache, hypotension, tachycardia were potential risks which has been cleared to participants.

Provision of Privacy

There were adequate provisions to maintain privacy of participants and confidentiality of the data, the patient name has been replaced by serial number & her address was confidential.

Statistical Analysis

The data were tested for normality with the Kolmogorov–Smirnov test with a significance level of 5%. ANOVA for paired samples was used to compare changes in mean of UtA, UA and MCA RI, as well as changes in maternal blood pressure before and after administration of GTN. Tukey's test was used for post-hoc analysis, with a significance level of $P < 0.05$. Statistical analysis was performed using SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

This study was carried on (50) singleton pregnancies meeting the inclusion criteria in department of Obstetrics & Gynecology in University Hospital of Tanta. The fifty patients were classified into the following two groups:

One patient in group (A) suffered from sudden intrauterine fetal death. Two patients in group (B) refused to accept administration of the drug, and one did not follow correctly the indications for patch application. Two patients in group (B) (8%) and one in group (A) (4%)complained of severe headache and stopped drugs administration. And all was removed from the data analysis. Group (A) n=23 and Group (B) n=20

The demographic data and hemoglobin of the two study groups showed in (table 1) with no statistically significance between the two study groups.

Comparing the two study groups, it was found that the mean arterial blood pressure in sildenafil group(A) was 95.5 ±4.3841, with range between 85 and 105 before medication and 88.8±4.3841on the day after medication with range 81-97 with statistically significant variation as there was decrease (7%).

The 21th day after medication the mean arterial blood

Table 1. *The demographic data of the two study groups:*

	Age (years)		BMI (kg/m²)		Gestational age (Weeks)		HB% (gm/dl)	
Groups	Sildenafil (n=23)	transdermal nitroglycerin patch (n=20)	Sildenafil (n=23)	transdermal nitroglycerin patch (n=20)	Sildenafil (n=23)	transdermal nitroglycerin patch (n=20)	Sildenafil (n=23)	transdermal nitroglycerin patch (n=20)
Range	22 – 35	20 – 31	26 – 30	25-29	24-33	25-33	11.1 – 12.5	11-12.4
Mean ±SD	27.21 ±4.41	26.45±3.705	28.478±1.081	28.85±2.6212	28.9565±3.509	29.65±2.1588	11.6 ±0.5	11.5 ±0.4
p. value	0.54369		0.631		0.448077		0.270942	

Comparing the two study groups according to age, body mass index, mean gestational age per weeks and mean HB%(gm/dl) they were statistically non-significant.

pressure was 86.6±4.8601 with range between 80 and 95, with-statistically non-significant variation in MAP between the day and 21th day after medication but a significant reduction (9%)in MAP between the day before medication and 21th day after medication The mean arterial blood pressure with nitrodermal patch group (B) was 94.5±4.67, with range between 85 and 105 before medication, and 79.04±5.904 on the day after medication with range 70-92 with statistically significant reduction 16%.

The 21th day the mean arterial blood pressure was 77.08 ±5.48 with range between 65 and 90 with statistically non-significant variation in MAP between the day after medication and 21th day but significant(18%) reduction of MAP than before medication.

There was a significant difference between the two groups in MAP in the day after medication and 21th day of drug usage (*p*-value<0.001*) while there was no significant difference between the 2 groups at the study starting (*p*-value=0.5179) as showed in figure (1) and tables 2,3.

Comparing the two study groups, it was found that the mean umbilical artery (RI) in sildenafil group (A) was 0.757±0.03 before medication, 0.66±0.023 on the day after with statistically significant variation between them. On 21th day the mean umbilical artery (RI) was 0.649±0.02 with statistically non-significant variation between the day after medication and 21th day.

The mean umbilical artery (RI) with nitrodermal patch group (B) was 0.780±0.020, before medication, and 0.630±0.02040 on the day after medication with statistically significant variation between them, on 21th daythe mean umbilical artery (RI) was

Figure 1. *The Trial Design*

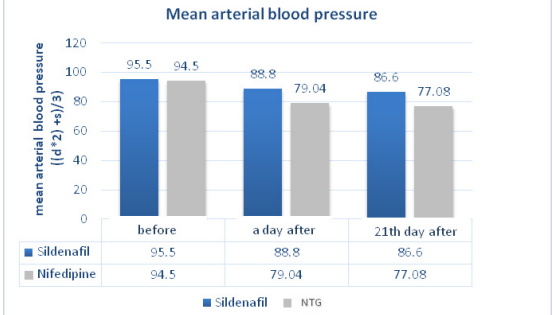

Table 2, 3. *The variant reduction in mean arterial blood pressure (MAP) ((d*2) +s)/3 between the two study groups and p-values.*

Variant reduction in MAP	Mean arterial blood pressure ((d*2) +s)/3 with sildenafil (n=23)	Mean arterial blood pressure ((d*2) +s)/3 with nitrodermal patch (n=20)
a day after	7%	16%
21th day after	9%	18%
difference	2%	2%
p value	P1	<0.001*
	P2	<0.001*
	P3	0.1410
	P4	<0.001*
	P5	<0.001*
	P6	0.2648
	P7	0.51790
	P8	<0.001*
	P9	<0.001*

P1: MAP* group A before and a day after medication
P2: MAP* group A before & 21thday after medication
P3: MAP* group A a day after & 21thday after medication
P4: MAP* group B before and a day after medication
P5: MAP* group B before & 21thday after medication
P6: MAP* group B a day after & 21thday after medication
P7: MAP* group A&B before medication
P8: MAP* group A&B a day after medication
P9: MAP* group A&B 21th day after medication

Table 4. *The umbilical artery resistance index (RI) of the two study groups*

Variant reduction in MAP	Umbilical a. R I with sildenafil (n=23)			Mean arterial blood pressure ((d*2) +s)/3 with nitrodermal patch (n=20)		
	before	a day after	21th day	before	a day after	21th day
Mean + SD	0.757 ±0.03	0.66 ±0.023	0.649 ±0.02	0.780 ± 0.020	0.630 ±0.02040	0.631 ±0.0169
Variation %	12%			19%		
p value	P1			<0.001*		
	P2			<0.001*		
	P3			0.137923		
	P4			<0.001*		
	P5			<0.001*		
	P6			0.860424		
	P7			0.079970		
	P8			0.000187*		
	P9			0.006892*		

P1: UA RI* group A before and a day after medication
P2: UA RI* group A before & 21thday after medication
P3: UA RI* group A a day after & 21thday after medication
P4: UA RI* group B before and a day after medication
P5: UA RI* group B before & 21thday after medication
P6: UA RI* group B a day after & 21thday after medication
P7: UA RI* group A&B before medication
P8: UA RI* group A&B a day after medication
P9: UA RI* group A&B 21th day after medication

Table 5. *Middle cerebral artery (RI) of the two study groups.*

	Uterine a. (R I) with sildenafil (n=23)			Uterine a. (R I) with nitrodermal patch (n=20)		
	before	a day after medication	21th day after medication	before	a day after medication	21th day after medication
Mean + SD	0.877 ± 0.0187	0.8689±0.0158	0.833 ±0.16	0.877 ± 0.0187	0.8689±0.0158	0.631 ±0.0169
Variation %	12%			19%		
p value	P1			0.790738		
	P2			0.185223		
	P3			0.172161		
	P4			0.92010		
	P5			0.207888		
	P6			0.20678		
	P7			0.784688		
	P8			0.991033		
	P9			0.938211		

P1: UA RI* group A before and a day after medication
P2: UA RI* group A before & 21th day after medication
P3: UA RI* group A a day after & 21th day after medication
P4: UA RI* group B before and a day after medication
P5: UA RI* group B before & 21th day after medication
P6: UA RI* group B a day after & 21th day after medication
P7: UA RI* group A&B before medication
P8: UA RI* group A&B a day after medication
P9: UA RI* group A&B 21th day after medication

Table 5. *uterine artery (RI) of the two study groups*

	Uterine a. (R I) with sildenafil (n=23)			Uterine a. (R I) with nitrodermal patch (n=20)		
	before	a day after medication	21th day after medication	before	a day after medication	21th day after medication
Mean + SD	0.58873 ±0.011178	0.484759 ±0.051677	0.476475 ±0.02518	0.58525 ±0.007856	0.476069 ±0.005223	0.466667 ±0.007827
Variation %	21% / 23%			22.5% / 24%		
p value	P1			<0.001*		
	P2			<0.001*		
	P3			0.024398*		
	P4			<0.001*		
	P5			<0.001*		
	P6			<0.001*		
	P7			0.321151		
	P8			0.007359*		
	P9			0.001431*		

P1: UtA RI* group A before and a day after medication
P2: UtA RI* group A before & 21th day after medication
P3: UtA RI* group A a day after & 21th day after medication
P4: UtA RI* group B before and a day after medication
P5: UtA RI* group B before & 21th day after medication
P6: UtA RI* group B a day after & 21th day after medication
P7: UtA RI* group A&B before medication
P8: UtA RI* group A&B a day after medication
P9: UtA RI* group A&B 21th day after medication

Table 7. *Abdominal circumference, amniotic fluid index and estimated fetal weight according to the two study groups.*

Sildenafil parameters	Abdominal circumference (mm)	Amniotic fluid index (cm)	Estimated fetal weight (gm)	comparison between the two groups (p-value)	
Before treatment mean ± standard deviation	218.739 ± 31.2995	7.917391 ±0.816674	1180.609 ±438.8864	P1	0.539398
				P2	0.363694
				P3	0.1562
After treatment (21th day) Mean ± standard deviation	246.087 ±29.33337	8.478261 ±0.605247	1597.87 ±564.33	P4	0.828752
				P5	0.705847
				P6	0.10317
Variations %	Increased 11%	Increased 6.6%	Increased 26%		
P-value	0.003789*	0.0021*	0.007579*		
Nitrodermal patch parameters	Abdominal circumference (mm)	Amniotic fluid index (cm)	Expected fetal weight (gm)		
Before treatment mean ± standard deviation	223.75 ±19.4635	7.984210 ±0.57608	1225.3 ±310.045		
After treatment (21th day) Mean ± standard deviation	253.05 ±18.17017	8.745 ±1.17495	1749.7 ±400.61		
Variations %	Increased 12%	Increased 8.5%	Increased 30%		
P-value	<0.001*	<0.001*	<0.001*		

P1: AC group A&B in 1st day
P2: AC group A&B in 21th day
P3: AFI group A&B in 1stday
P4: AFI group A&B in 21thday
P5: EFW group A&B in 1stday
P6: EFW group A&B in 21thday

0.631±0.0169 with statistically non-significant variation between the day after medication and 21th day. There was non- significant difference between the 2 groups in umbilical artery (RI) (*p*-value 0.079970)on 1st measurement. Variant reduction between RI before& a day after medication was 12% in group (A) and 14% between RI before & 21th day after medication. There was a variant decrease 19% in group (B) in mean umbilical artery (RI) between RI before & 21th day after medications showed in table(4).

Comparing the two study groups, it was found that no significant variation between the two groups, and in the same group in middle cerebral artery resistance index (MCA RI) before, a day after medication and 21th day after medication as showed in table 5.

Comparing the two study groups, it was found that the uterine artery (RI) in sildenafil group (A) was 0.58873±0.011178 before medication, and 0.484759±0.051677 on the day after medication with statistically significant variation (*p*-value<0.001*), on 21th day the mean uterine artery (RI) was 0.476475±0.02518 with statistically significant variation between the day after medication and 21th day after medication (*p*-value <0.05).

The uterine artery (RI) with nitrodermal patch group (B) was 0.58525±0.007856, before medication, and 0.476069±0.005223 on the day after medication with statistically significant variation, on 21th day the mean uterine artery (RI) was 0.466667±0.007827 with statistically significant variation between the day after medication and 21th day after medication. There is a no significant difference between the 2 groups in uterine artery (RI) (*p*-value 0.321151) at the study starts but there was a significant difference between the two groups after drugs administration (*p*-value <0.05). Variant reduction before drug administration & the day after treatment was 21% in group (A) and 23% between the uterine artery (RI)before and 21th day after medication. There was a variant decrease 22.5% in group (B) in umbilical artery (RI)before the drug administration

& the day after treatment, and 24% between the uterine artery (RI) before and 21th day after medication as showed in table(6).

There was a significant increase in abdominal circumference, fetal weight and AFI after 3 weeks of using the two drugs as (*p*-value <0.05). The comparison between the two groups showed non-significant difference as showed in table 7.

DISCUSSION

The study included (fifty) singleton pregnant women with age between (20 to 35) years old, gestational age between 24 to 33 weeks, Hb % > 11gm/dl, body mass index "between" (22 to 30), and suffering from asymmetrical intrauterine growth restriction that resulted from placental insufficiency (diagnosed by U/S measures fetal abdominal circumference < 5th percentile for gestational age, high Doppler resistance indices of umbilical and uterine arteries and normal fetal middle cerebral Doppler indices).Symmetrical intrauterine growth restrictions due to fetal anomalies, chromosomal anomalies and congenital infection was excluded by history taking and 2D and\or 4D U/S anomaly scanning performed before the study.

Gestational age had been calculated from the date of the last menstrual period or ultrasound examination performed during the first trimester of the pregnancy.

Then Patients had been randomized into two groups :(A) sildenafil group and (B) transdermal nitroglycerin group, based on blocked randomization with opaque envelop. Color Doppler ultrasonography had been performed. Estimation of fetal weigh, abdominal circumference and amniotic fluid index were measured before and 3 weeks after receiving the medications.

At the start of the study there were no significance differences between two standard groups as regards the demographic DATA, Doppler indices, AFI, EFW and Abdominal circumference.

Sildenafil citrate had been administrated orally at a dose of 25 mg three times daily for 21 days. A new 50-mg transdermal nitroglycerin patch had been applied to the abdominal skin at 7:00 am or on awaking for sixteen hours per day for 21 days, women had been advised to change the site of application of transdermal nitroglycerin patches and warned about headache and slight skin erythema, and patients had been asked about the complications

A patient in group (A) suffered from sudden intrauterine fetal death. Two patients in group (B) declined to accept administration of the drug, and one did not follow correctly the indications for patch application. Two patients in group (B) and one in group (A) complaint of severe headache and stopped drugs administration.And all was removed from the data analysis. Group (A) n=23 and Group (B) n=20.

There was a statistically significant reduction (7%) in the mean arterial blood pressure in sildenafil group (A)in the day after receiving medication, on 21th day, 9% reduction of MAP than before medication. With no significant difference between the day after receiving medication and 21th day,

Group (B):nitrodermal patch group. There was a statistically significant reduction (16%) in the mean arterial blood pressure)in the day after receiving medication, on 21th day, (18%) reduction of MAP than before medication. With no significant difference between the day after receiving medication and 21th day.

Abdominal circumference, AFI and estimated fetal weight were significantly increased after 21 days from treatment, with no significant difference between the two groups.

The Doppler study showed a significant reduction in umbilical artery RI, uterine artery RI in the two groups in the day after medication and 21th day. But no significant changes in concern with the middle cerebral artery RI was observed and no significant difference between the two groups.

`TRAPANI Jr, et al.[9] that performed a study on 35 singleton pregnancies (gestational age range: 24-31 weeks) with IUGR and abnormal uterine and umbilical artery Doppler waveforms. Maternal arterial blood pressure as well as Z-scores for the pulsatility index (PI) of the uterine, umbilical and fetal middle cerebral arteries (MCA) before and after application of a transdermal nitroglycerin patch (average dose 0.4 mg/h), oral sildenafil citrate (50 mg) or placebo was measured. The mean arterial blood pressure with GTN was 110±6.9 at the start then decreased to 98±6.1 with variation (10.9%) and p-value <0.05. And with sildenafil was 108±7.1 at the start then decreased to 92±5.6 with variation(14.5%), p-value<0.05. While placebo showed non-significant changes with variation(3.5%). Also, the study showed a significant decrease in uterine artery PI with both GTN (21.3%) and sildenafil citrate (20.2%). A significant reduction in umbilical artery PI was also observed for both GTN (19.2%) and sildenafil citrate (18.4%). No difference in Doppler PI was observed for uterine and umbilical arteries when GTN and sildenafil groups were compared. No Doppler velocimetry changes were observed for the placebo group. No significant change in MCA PI was observed in any of the groups. These results are in accordance with our results in this study

Also, in Diego Gazzolo, et al.[10] study was done on 51 pregnant women (gestational age, 27-35 weeks) with IUGR fetuses and impaired uteroplacental blood flow. Patients were assigned, by use of computer-generated random numbers, to receive either placebo (n=25) or transdermal glyceryl trinitrate (Nitroderm TTS; Ciba-Geigy) at a dose of 5 mg/16 h daily until delivery (n=26). Control group consisted of 20 apparently healthy fetuses matched for gestational age at sampling and with birth weights between the 10th and 90th percentiles.The flow velocity waveforms of the main branch of the uterine artery bilaterally, the umbilical artery (UA), and fetal middle cerebral artery (MCA) were recorded by means of a duplex pulsed color Doppler ultrasound (SSD-2000; Aloka). Transdermal glyceryltrinitrate administration was associated with a significant decrease in uterine artery RI and the UA PI (p<0.05), whereas no significant difference was found in MCA PI (p>0.05). In the placebo group, Flow Velocity Waveforms (FVWs) worsened

with a significant increase in the uterine artery RI (p<0.05), this produced a higher mean gestational age at delivery in the treated than in the placebo group. And that gives strength to the study results.

Also, Lin et al.[11] reported a decrease in uterine artery pulsatility index and resolution of uterine artery notching following administration of sildenafil citrate to a case of IUGR diagnosed at 26 weeks of gestations. they also observed increase in EFW without maternal or neonatal adverse outcomes.

Other study agrees with our results according to abdominal circumference, Von Dadelszen, et al.[12] tested the potential for sildenafil to improve fetal growth in an open-label pilot study. Ten women with pregnancies affected by severe early-onset FGR, where the chance of intact fetal survival was felt to be less than 50%, accepted the option of taking 25-mg sildenafil TDS. Outcomes were compared with pregnant women fulfilled the treatment criteria but either declined or were not offered Sildenafil (n=17). The results showed that Sildenafil treatment was associated with increased post-treatment fetal growth velocity in the AC [9/10 (treated) vs7/17 (control); odds ratio, 12.9; 95% CI, 1.3, 126],in agree with our study that showed a significant increase in abdominal 3 weeks of using the two drugs.

Sildenafil citrate treatment in women suffering from IUGR showed significant results in this study like ElsayedElbadawy, et. al.[13], a study involved 30 patients who presented to Shatby Maternity University Hospital, they were 26-32weeks with singleton spontaneous pregnancy, who were diagnosed as intrauterine growth restriction, they divided into two groups: study group (n=15); women who received 20 mg sildenafil citrate oral tablets for 6 weeks, control group (n=15); women who received placebo. Follow-up was done for 4-6 weeks. Doppler study of fetal blood vessels including umbilical artery (UA), middle cerebral arteries (MCA) and ductus venosus (DV) weekly using Voluson P8 ultrasound machine [GE].Cases of study and control groups were matched in age, gestational age, gravidity, parity, abortion, blood pressure, weight, body mass index, estimated fetal weight and amniotic fluid index.

In agreement to results founded, ElsayedElbadawy,et. al.[13] results showed significant statistical difference between umbilical arteries [UA] indices in sildenafil treated cases and control. Mean umbilical artery systolic/diastolic ratio (UA S/D) significantly decreased in the Sildenafil group as compared to the placebo group at the end of trial (p=0.047). Also, mean umbilical artery pulsatility index (UA PI) significantly decreased in the Sildenafil group in comparison with the placebo group (p=0.026).

But Contradictory to our findings, regarding MCA Doppler study, the MCA PI between cases and control, mean MCA PI significantly higher in sildenafil group in comparison with placebo group p=0.001. Also, cerebroplacental ratio significantly decreased at the end of study in control group compared to cases group (p=0.001). Also, there was no significant statistical difference between the rate of increase in AC per week or EFW per week between case and control group. Also, there was no significant statistical difference between measurements of AFI between cases and control group at the end of the study. However, the sildenafil dose was smaller and smaller study group number, and it is unclear whatever the study and control groups suffering from symmetrical or asymmetrical IUGR.

Despite a few negatives studies, sildenafil ctitrate has shown promise in vitro as well as in animal studies in the treatment of both IUGR and pre-eclampsia. Wareing et al.[14] conducted a study where small artery dissected from myometrial biopsies obtained at cesarean section from normal pregnant women (n=27) or women whose pregnancies were complicated by FGR (n=12) were mounted on wire myographs. Vessels were constricted (with arginine vasopressin or U46619) and relaxed (with bradykinin) before and after incubation with a phosphodiesterase-5 inhibitor, sildenafil citrate. They concluded that sildenafil citrate improves endothelial function of myometrial vessels from women whose pregnancies are complicated by intrauterine growth restriction.

CONCLUSION

Our study showed a highly significant benefit of using sildenafil citrate and transdermal nitroglycerin in treatment of cases of asymmetrical IUGR, as a significant increase in placental flow observed from decreasing the uterine and umbilical arteries Doppler indices, also a significant increase in abdominal circumference, AFI and EFW. So, the results of this small trial are sufficiently encouraging to use sildenafil citrate and NTG as treatments of non-complicated IUGR cases, and to justify further more large trials to assess evidence biased management of IUGR.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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