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Comparative Study between the Effect of oral Sildenafil Citrate Versus Oral Nitroglycerin on Intrauterine Growth Restriction in Normotensive Pregnant Women

Obstetrics & Gynecology

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ABSTRACT

Background: Severe perinatal morbidity and mortality are increased by severe early-onset intrauterine growth restriction., especially when combined with iatrogenic premature delivery. It causes complications in about 0.2 percent of pregnancies. Small-for-gestation newborns have birth weights or lengths that are less than the 10th percentile for gender and gestational age., and these babies are constitutionally small.

Aim of the work: To compare the effects of oral sildenafil citrate 20 mg and oral nitroglycerin 2.5 mg in normotensive pregnant females with intrauterine growth restriction (IUGR).

Patients and methods: This prospective observational study was performed on a total of 100 pregnant normotensive females diagnosed with IUGR in Al-Hussein University Hospitals and Dar Ismail Hospital for Obstetrics and gynecology, Alexandria, Egypt, from May 2020 to May 2021 with inclusion and exclusion criteria.

Results: The age disparity between the two study groups was not statistically significant. The mean (standard deviation) age in years for group I is 26.20 2.75 and 26.70 3.16 for group II. The P-value is 0.439. In terms of body mass index, there was no significant difference between the two groups studied (BMI). The mean (standard deviation) BMI (kg/m2) for group I is 35.51 3.55 and 34.59 3.27 for group II. The probability is 0.182. There was a statistically significant difference in parity between the two groups studied. According to biparietal diameter (BPD) in mm, Before and after 14 days of treatment, there was a significant difference in both groups. There was a significant difference in both groups' head circumference (HC) in mm before and after 14 days of treatment. There was a significant difference in both groups' abdominal circumference (AC) in mm before and after 14 days of treatment. The length of the femurs differed significantly.(FL) in both groups before and after 14 days of treatment.

Conclusion: The current study concluded that using oral Sildenafil citrate and oral Nitroglycerin in the treatment of asymmetrical IUGR has a high significance, By reducing the uterine and umbilical arteries, a significant increase in placental blood flow was observed .

Doppler characteristics. Sildenafil citrate may be preferred over oral Nitroglycerin due to fewer side effects.

Keywords: *Intrauterine Growth Restriction; Oral Sildenafil Citrate; Oral Nitroglycerin.*

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INTRODUCTION

Severe perinatal morbidity and mortality are increased by severe early-onset intrauterine growth restriction. especially when combined with iatrogenic premature delivery. It complicates about 0.2 percent of pregnancies[1]. In small-for-gestation newborns, These babies are constitutionally small because their birth weight and/or length are below the 10th percentile for gender and gestational age [2]. Long-term neurodevelopmental and neurological disorders, as well as foetal distress, asphyxia, neonatal encephalopathy, hypothermia, hypoglycemia, and poor feeding, are more common in IUGR foetuses. [3]. Intrauterine growth restriction is the second most common cause of perinatal morbidity after prematurity. [4] Uterine blood flow increases dramatically during a normal pregnancy, from about 50 ml/min at 10 weeks' gestation to over 1200 ml/min at term [5]. Maternal vascular resistance in the uterine arteries increased in some pregnancies with intrauterine growth restriction, resulting in poor foetal growth. When resistance levels are

normalized, such pregnancies have a much better outcome [6].

The trophoblast produces nitric oxide during a normal pregnancy. , which improves oxygen and nutritional supply to the foetus by assisting vasodilation in the fetoplacental circulation [7]. Nitric oxide relaxes the smooth muscle of the arterial and venous circulation and may prevent platelet aggregation and adhesion. Nitric oxide donors, which act as vasodilators, have the potential to be a promising therapeutic strategy for embryo development and foetal growth. [7]. Chronic hypoxia has no effect on the umbilical vein endothelial cells in IUGR, which may result in fetoplacental vasoconstriction. Nitric oxide, as a locally potent vasodilator, aids in perfusion regulation by offsetting the effects of other vasoactive agents [8]. Nitroglycerin (Glyceryltrinitrate, GTN) is a biotransformation pathway that produces nitric oxide. Tolerance development is one of its limitations. One of the few reported side effects is headache [9].In vitro, phosphodiesterase inhibition caused a reversible increase in myometrial arterial tone in pregnancies with foetal growth restriction but no preeclampsia [10]. Noninvasive Doppler ultrasound velocimetry has revealed decreased flow or increased resistance in the uterine and umbilical arteries in pregnancies with foetal growth restriction, resulting in decreased uteroplacental flow. [11] Sildenafil citrate is a selective cyclic guanosine monophosphate (cGMP) inhibitor as well as a phosphodiesterase-5 (PDE-5) inhibitor. It improves the relaxation and accumulation of cyclic guanosine monophosphate (cGMP) induced by exogenous and neurally released nitric oxide in the corpus cavernosum [12].

Sildenafil citrate improves estrogen-induced vasodilation and stimulates uterine blood flow [13]. It has shown great promise as a pulmonary vasodilator [14]. Sildenafil citrate has been proposed as a possible treatment for pulmonary hypertension during pregnancy, a condition associated with poor maternal and foetal outcomes [15]. A growth-restricted foetus whose mother is taking Sildenafil for pulmonary hypertension has grown stronger [16]. In normal pregnancy women and pregnant women with foetal growth restriction, sildenafil citrate administration reduces the effects of vasoconstrictors on myometrial small arteries [17]. While sildenafil citrate's placental transfer has not been quantified, its chemical properties indicate that it will easily cross the placenta into the foetus [18]. As a result, sildenafil citrate may be a promising therapeutic option for improving uteroplacental blood flow in human pregnancies complicated by severe IUGR. [19].

The aim of the study is to compare the effect of oral sildenafil citrate 20 mg and oral nitroglycerin 2.5 mg in cases of intrauterine growth restriction (IUGR) in normotensive pregnant females.

PATIENTS AND METHODS

This prospective observational study received ethical committee approval and written consent from the patients.study was performed on a total of 100 pregnant normotensive females diagnosed with IUGR in Al-Hussein University Hospitals and Dar Ismail Hospital for Obstetrics and gynecology, Alexandria, Egypt, from May 2020 to May 2021.

Study population: pregnant normotensive females diagnosed with IUGR in Al-Hussein University Hospitals and Dar Ismail Hospital for Obstetrics and gynecology, Alexandria, Egypt, with the following inclusion criteria:

Inclusion criteria: Age < 21 years, Singleton pregnancy, Between 28 and 32 weeks, Patients sure of date, with fetal growth restriction of likely placental origin and with abnormal umbilical artery Doppler.

Exclusion criteria: Chronic hypertension, Preeclampsia /Eclampsia, Gestational DM, Thyroid disorders, Past history of IUGR, Chronic renal disease, Anti-coagulant therapy and Known intolerance to Sildenafil or Nitroglycerin.

Study Procedures:

All patients were subjected to the following procedures: history taking, clinical examination, and investigations., treatment by each one of two drugs alone and finally follow up the effect of each drug on patients to compare between their effect.

History taking:

Full history taking from each patient including personal history, obstetric history, medical history and surgical history of each patient and last menstrual period to calculate gestational age and compare it with the gestational age calculated from ultrasound biometry and the gestational age calculated from symphysis fundal length.

Personal history, including age, BMI.

Obstetric history, including previous IUGR, accurate pregnancy dating from last menstrual period.

Medical history as hypertension, diabetes, obesity, drug use, smoking, and chronic diseases such as renal, hepatic, or collagenic disorders

Surgical history as previous cesarean section due to IUGR

Clinical examination:

General examination including blood pressure measurement to exclude hypertensive patients.

Obstetric examination, including symphysis fundal length to correlate with gestational age measured by calculation from last menstrual period.

Investigational studies:

Laboratory investigation:

TSH, T3 and T4 to exclude hyper and hypothyroid patients,

Hour Gestational Diabetes Test (O'sullivan test) and oral glucose tolerance test to exclude diabetic patients.

Radiological investigation:

Ultrasound examination.

Doppler velocimetry was performed on GE Voluson P8 (General Electric Medical Systems) ultrasound scanner, using a 3.75-MHz convex transducer.Fetal biometry includes sonographic measurements of various anatomical segments of the fetus. according to the Hadlock formula, including (Biparietal Diameter), (head circumference), (abdominal circumference), (femur length.Trans-cerebellar Diameter), and EFW (estimated foetal weight). [log10 EFW = 1.3596 – 0.00386(AC x FL) +0.0064 (HC)+0.00061(BPD x AC) + 0.0425(AC) + 0.174(FL)].

Fetal presentation, Fetal activity (breathing movement), and amount of amniotic fluid,

Doppler ultrasound study of the uterine artery, umbilical artery and middle cerebral artery, measuring:

Pea k syst olic velocity , End diastolic velocity , and Time averaged .

Systolic velocity/diastolic velocity . Resistive index = (PSV-EDV) / PSV.

Pulsatility index = (PSV-EDV) / TAV.

Treatment:

Group A (50 patients) received oral Sildenafil 20 mg three times daily for 14 days. Drug used is Respatio 20 mg by Pharma Right Group.

Group B (50 patients) received oral Nitroglycerin 2.5 mg two times daily for 14 days. Drug used is Nitro MAK retard 2.5 mg by October Pharma S.A.E.

Sample Size: The sample size is calculated using epi-info 9 by adjusting the power of the test to 80% and confidence interval to 95% with a margin of error accepted adjusted to 5% depending on From March 2016 to October 2017, a prospective non-randomized study was conducted at Mansoura University Hospitals. [20]. In this study, mean of birth weight (gm) in the group receiving Sildenafil was 2066.8 ± 351.6 and 1732.8 ± 360.8 in the control group. The minimum calculated sample size is 36 (18 for each group). By adding 10% as nonresponse rate, the minimum calculated sample size of 40 will be appropriate.The study included 100 pregnant normotensive females diagnosed with IUGR.

Outcome measures:

The primary outcome: Ultrasound biometry and Doppler study was calculated and measured at start of study and after 14 days of receiving treatment.We considered that the baby got benefits from the drug when the EFW increased and the RI decreased, when this occurred, we continued the drug and the study, when not occurred we stopped the drug.

Secondary outcome: The patients who improved by treatment continued receiving the drugs till delivery to estimate gestational age at time of delivery in weeks, route of delivery, birth weight, neonatal outcome and APGAR score.

Ethical Considerations: The patient data were anonymous. Data presentation were not be by the patient's name but by diagnosis and patient confidentiality was protected. All participants signed an informed consent form in Arabic, which was confirmed by date and time. confidentiality was preserved by assigning a number to patients initials and only the investigator knew it

Conflict of interest: the candidate declared that there is no conflict of interest and the cost of the study was paid by the candidate.

Statistical analysis: The data was entered into a computer and analysed using IBM SPSS version 20.0 software. The headquarters of IBM Corporation are in Armonk, New York. To describe qualitative data, numbers and percentages were used. To describe quantitative data, the terms range (minimum and maximum), mean, standard deviation, and median were used. The significance of the obtained results was calculated at the 5% level.

RESULTS

This study includes 100 pregnant normotensive females diagnosed with IUGR divided into two groups with following study.
Group I (50 patients) received oral Sildenafil 20 mg
Group II (50 patients) received oral Nitroglycerin 2.5 mg

Age (years)	Group I (n= 50)		Group II (n= 50)		Test of sig.	P
	No.	%	No.	%		
21 – 25	20	38.0	18	36.0	χ^2= 3.079	^{MC}p= 0.403
26 – 30	27	52.0	29	58.0		
>30	3	4.0	3	6.0		
Min. – Max.	19.0 – 31.0		22.0 – 34.0			
Mean ± SD.	26.20 ± 2.75		26.66 ± 3.16		t= 0.777	0.439
Median (IQR)	26.0 (25 - 28)		27.0 (24 - 28)			

Table 1: Comparison between the two studied groups according to age in years.
Table (1) shows that there was no significant difference between the two studied groups according to age. Mean (±SD) age in years for group I is 26.20 ± 2.75 and 26.70 ± 3.16 for group II. P value is 0.439.

EFW (gm)	Before treatment	After treatment	t_p	p_1
Group I (n= 50)				
Min. – Max.	1090 – 2099	1157 – 2229	34.117*	<0.001*
Mean ± SD.	1554.0 ± 275.64	1686.36 ± 276.67		
Median (IQR)	1524.0 (1398 – 1663)	1685 (1521 - 1825)		
Group II (n= 50)				
Min. – Max.	1032 - 2168	1140 – 2301	48.174*	<0.001*
Mean ± SD.	1520.54 ± 395.32	1640.84 ± 402.09		
Median (IQR)	1387.0 (1169 - 1861)	1512.50 (1260 - 1983)		
t_S	0.491	0.659		
p_2	0.625	0.511		

Table 2: Comparison between the two studied groups according to EFW before and after two weeks of treatment
Table (2) shows significant difference in both groups before treatment and after 14 days of treatment according to expected fetal weight (EFW) in gm.Mean (±SD) EFW in group I before treatment is 1554.0 ± 275.64 and 1686.36

± 276.67 after treatment. P value is <0.001.Mean (±SD) EFW in group II before treatment is 152.54 ± 395.32 and 1640.84 ± 402.09 after treatment. P value is <0.001.But there is no significant difference between the two groups before treatment with P2 value 0.625 and after treatment with P value 0.511.

	PI	Before treatment	After treatment	Test of sig.	p_1
Uterine Artery	Group I (n= 50)				
	Min. – Max.	1.65 – 2.01	1.17 – 1.57	Z=303.513*	<0.001*
	Mean ± SD.	1.82 ± 0.14	1.35 ± 0.14		
	Median (IQR)	1.86 (1.69 – 1.90)	1.39 (1.22 – 1.44)		
	Group II (n= 50)				
	Min. – Max.	1.61 – 2.01	1.12 – 1.58	Z=247.01*	<0.001*
	Mean ± SD.	1.77 ± 0.16	1.30 ± 0.17		
	Median (IQR)	1.69 (1.63 – 1.90)	1.22 (1.15 – 1.43)		
	U	926.0*	938.50*		
	p_2	0.024*	0.031*		
Umbilical artery	Group I (n= 50)				
	Min. – Max.	1.22 – 1.61	0.94 – 1.35	Z=6.337*	<0.001*
	Mean ± SD.	1.45 ± 0.14	1.19 ± 0.15		
	Median (IQR)	1.50 (1.45 – 1.65)	1.23 (1.32 – 1.58)		
	Group II (n= 50)				
	Min. – Max.	1.30 – 1.67	1.01 – 1.44	Z=6.232*	<0.001*
	Mean ± SD.	1.52 ± 0.12	1.25 ± 0.13		
	Median (IQR)	1.50 (1.64 – 1.99)	1.24 (1.41 – 1.61)		
	U	998.50	942.50*		
	p_2	0.080	0.033*		
Middle cerebral artery	Group I (n= 50)				
	Min. – Max.	1.40 – 2.24	1.30 – 2.33	Z=2.572*	0.010*
	Mean ± SD.	1.67 ± 0.28	1.69 ± 0.31		
	Median (IQR)	1.64 (1.45 – 1.64)	1.68 (1.46 – 1.72)		
	Group II (n= 50)				
	Min. – Max.	1.45 – 2.03	1.39 – 2.81	Z=1.820	0.069
	Mean ± SD.	1.86 ± 0.19	1.91 ± 0.29		
	Median (IQR)	1.99 (1.64 – 1.99)	1.98 (1.62 – 2.06)		
	U	696.50*	769.0*		
	p_2	<0.001*	<0.001*		

Table 3: Association between the two studied groups according to PI before and after two weeks of treatment studied groups.

Table (3) shows major variance in both groups before treatment and after 14 days of treatment according to pulsatility index (PI) in uterine artery and Umbilical artery but no significant difference in Middle cerebral artery.

Mean (±SD) PI in group I before treatment is 1.82 ± 0.14 in uterine artery, 1.45 ± 0.14 in umbilical artery and 1.67 ± 0.28 in middle cerebral artery. After treatment mean RI is 1.35 ± 0.14, 1.19 ± 0.15 and 1.69 ± 0.31 respectively. P value is <0.001 for uterine artery, < 0.001 for umbilical artery and 0.010 for middle cerebral artery.

Mean (±SD) PI in group II before treatment is 1.77 ± 0.16 in uterine artery, 1.52 ± 0.12 in umbilical artery and 1.86 ± 0.19 in middle cerebral artery. After treatment mean RI is 1.30 ± 0.17, 1.25 ± 0.13 and 1.91 ± 0.29 respectively. P value is <0.001 for uterine artery, <0.001 for umbilical artery but 0.069 for middle cerebral artery.

But there is no significant difference between the two groups before treatment with P2 value 0.024 in uterine artery and 0.080 in Umbilical artery but there is significant difference in Middle cerebral artery wit P2 value <0.001. Also, there is no significant difference between the two groups after treatment with P2 value 0.031 in uterine artery and <0.001 in Middle cerebral artery but there is

Birth weight (Kg)	Group I (n= 50)	Group II (n= 50)	t	p
Min. – Max.	1.90 – 3.40	1.90 – 3.60	2.246*	0.027*
Mean ± SD.	2.58 ± 0.41	2.77 ± 0.43		
Median (IQR)	2.50 (2.20 – 2.80)	2.70 (2.55 – 2.95)		

Table 4: Comparison between the two studied groups according to birth weight.

Table (4) shows no significant difference between the two studied groups according to birth weight. Mean (±SD) birth weight in kilogram (Kg) for group I is 2.58 ± 0.41 and 2.77 ± 0.43 for group II. P value is 0.027.

Neonatal outcome	Group I (n= 50)		Group II (n= 50)		□□	p
	No.	%	No.	%		
Well baby	40	80.0	38	76.0	□□□□□	0.629
NICU	10	20.0	12	24.0		

Table 5: Comparison between the two studied groups according to neonatal outcome.

Table (5) shows no significant difference between the two studied groups according to neonatal outcome.

In group I 80% went to well-baby, 20% to NICU and no neonatal losses.

In group II 76% went to well-baby, 24% to NICU and no neonatal losses. P value is 0.629.

APGAR score	Group I (n= 50)	Group II (n= 50)	t	p
Min. – Max.	5.0 – 10.0	6.0 – 10.0	0.085	0.932
Mean ± SD.	8.86 ± 1.20	8.84 ± 1.15		
Median (IQR)	9.0 (8.0 – 10.0)	9.0 (8.0 – 10.0)		

Table 6: Comparison between the two studied groups according to APGAR score.

Table (6) shows no significant difference between the two studied groups according to Apgar score. Mean (±SD) Apgar score for group I is 8.86 ± 1.20 and 8.84 ± 1.15 for group II. P value is 0.932.

Side effects	Group I (n= 50)		Group II (n= 50)		□□	p
	No.	%	No.	%		
Headache	10	20.0	21	42.0	5.657*	0.017*
Dyspepsia	3	6.0	3	6.0	□□□□□	FEp=1.000
Flushing	5	10.0	6	12.0	□□□□□	0.749
Visual disturbance	9	18.0	13	26.0	□□□□□	0.334
Epigastric pain	6	12.0	10	20.0	□□□□□	0.275
Vomiting	5	10.0	7	14.0	□□□□□	0.538

Table 7: Comparison between the two studied groups according to side effects.

Table (7) shows that Headache was the most common side-effect: 10 (20%) cases in the sildenafil group, and 21 (42%) in the Nitroglycerine group (P = 0.017). In addition, there were 22 patients suffered from visual disturbances after administration of therapy; 9 in sildenafil group and 13 in Nitroglycerine group II (P=0.334). Also, five (10%) patients in the sildenafil group and six (12%) in the Nitroglycerine group had facial flushing (P = 0.749). Furthermore, three cases in each studied group had Dyspepsia. Moreover, there were 6 patients in sildenafil group and 10 patients in Nitroglycerine group had epigastric pain (P=0.275). Additionally, vomiting was detected in 5 (10%) women in sildenafil group and 7 (14%) in Nitroglycerine group (P=0.538).

DISCUSSION

This study was carried out on 100 pregnant women who attended to Al-hussein university Hospital and Dar Ismael Hospital antenatal care unit during the period from May 2020 to May 2021 to compare between Sildenafil citrate and Nitroglycerine as a vasodilator in cases of IUGR. All subjects were divided into 2 groups; group I included 50 participants who received 25 mg Sildenafil citrate daily and group II included 50 participants who received 5 mg Nitroglycerine daily.

The researchers looked at how Sildenafil citrate and nitroglycerin affected uterine, umbilical, and foetal middle cerebral artery Doppler indices, as well as changes in abdominal circumference, foetal weight, and amniotic fluid index, in patients with asymmetrical intrauterine growth restriction. In the current study, the age distribution of participants in both groups was comparable and nearly equal. The mean SD age of patients in the Sildenafil citrate group was 26.64 4.04 years, while it was 26.08 3.96 years in the Nitroglycerine group. There was no statistically significant difference in age (P=0.486).

Similarly, in the Mahmoud et al.[21] study, 90 singleton pregnancies with IUGR were randomly assigned to one of three groups: oral sildenafil citrate (50 mg), nitroglycerine patch (10 mg), or placebo. The mean age of the three groups was comparable with no significant difference as regards age was reported [21].

In contrast, in a prospective analytical study conducted over a period of 2 years on 60 pregnant females with IUGR, Manandhar et al.[12] The age group between 26 and 30 years was found to have the highest number of cases (38.3 percent), followed by the age group less than 20 years (25 percent) [22].

In the present study, the mean BMI in both groups was above the normal range. The mean BMI among the patients in the Sildenafil citrate group (27.9±4.9) was slightly higher among those in the Nitroglycerine group (26.28±5.1) with no statistically significant difference between both groups regarding BMI (P=0.109).

In a similar vein, El-Bheirey et al.[13] investigated BMI as a risk factor for IUGR in 50 women divided into Sildenafil (n=25) and Nitroglycerin (n=25) groups. They discovered that both groups' BMI means were above the normal range, with no statistically significant difference in BMI between the two groups. [23].

On the contrary, Manandhar et al.[12] found that among 60 pregnant women with IURG, The majority of cases (60%) had a normal BMI, as opposed to (36.71%) who had a lower BMI (22). A prospective Chinese study, on the other hand, discovered that infants born to women who were severely underweight before pregnancy with BMI 18 were at an increased risk of IUGR when compared to normal maternal BMI. [24].

We found that the mean ± SD of gestational age at the time of delivery was 34.31± 1.12 weeks in all studied cases. Most of the morbidity and mortality occurred between the gestational age between 32.1 and 35. In addition, gestational age means at the time of the first scan and at the delivery time were significantly lower in IUGR patients who received Nitroglycerine than that detected in patients who received Sildenafil citrate (P=0.009).

In a retrospective descriptive study of 73 pregnant females with IUGR, Sehested et al. agreed with our results. The average gestational age was reported to be 35.1 weeks. However, there was no statistically significant relationship between gestational age and degree of growth retardation (p = 0.50). [25]

In comparison, El-Bheirey et al.[13] found the mean gestational age of the Nitroglycerine group (29.65±2.15) was higher than those of the Sildenafil citrate group (28.9565±3.5), and, it was statistically non-significant [23].

In disagreement with our results, Trapani et al. in a prospective study of 35 singleton pregnancies with IUGR reported that the gestational age mean in IUGR patients who received Nitroglycerine (29.3 ± 2.4) was higher than the gestational age mean in patients who received Sildenafil citrate (28.5 ± 2.1) with no recorded statistically significant difference between both groups as regards the gestational age [9].

IUGR has been linked to a variety of maternal factors. It is widely accepted that Nulliparous women have a higher risk of IUGR by population centiles, with an OR ranging from 1.3 to 2.1 when compared to Multiparous women [26, 27]. Several studies have found that women who had an IUGR infant in a previous pregnancy were more likely to have an IUGR infant in their subsequent pregnancy. The recurrence rate was estimated to be around 20%.[28, 29].

According to the potential risk factors, most patients in the current study were parity 1 (33%), followed by parity zero (26%), then parity 2 and parity 3 (20%, and 17% respectively), and finally parity 4 (4%). In terms of parity, There was a statistically significant difference (p=0.02) between the two groups studied. In terms of previous IUGR, the majority of cases (63%) had none. There was also no statistically significant difference in the prevalence of previous IUGR between the two study groups (P=0.062).

Concerning the history of previous miscarriage, most of the cases (62%) had no history of miscarriage. No significant difference between the two studied groups was noted regarding the incidence of previous miscarriage (P=0.390) which was similar to 21. Mahmoud et al.[21] study that reported most women with IUGR had no previous miscarriage [21].

Various neonatal indicators for IUGR were reported in the current study, including low birth weight, neonatal sepsis, NICU admission, stillbirth, or perinatal death APGAR score < 7 in 5 minutes. The perinatal outcome was counted as adverse by the presence of one or more of the indicative outcomes. Comparison between the two studied groups as regards birth weight, neonatal sepsis, NICU admission, stillbirth, perinatal death, and APGAR score showed no statistically significant difference.

The mean ± SD of estimated fetal birth weight at admission in the Sildenafil group and the Nitroglycerine group were 964±104.02 and 927.6±108.1 respectively with no recorded statistically significant difference between both groups (P-value=0.089). This was in agreement with Trapani et al. study in which the estimated fetal birth weight was matched between the studied groups with no demonstrated statistically significant difference [9].

After management, the fetal weight improved in both groups. The mean ± SD of fetal birth weight in the Sildenafil group was 1824±218.82 and the Nitroglycerine group was 1824±218.82. This was similar to the study done by Muhammad et al.[19] where their mean birth weight was 1.8 ± 0.33 Kgs [29].

Most of our cases (72%) belonged to the birth weight range from 1500 to 2000 g compared to 7 subjects who remained under 1500 g. But, In terms of birth weight, there was no statistically significant difference between the two groups.

In comparison, in Manandhar et al.[12] study, After clinically confirmed IUGR, 60 cases were enrolled and received appropriate hospital management. The patients were admitted at various stages of pregnancy. Out of 60 clinically diagnosed cases, 36 (60.0 percent) of IUGR neonates had birth weights ranging from 2.5 to 3 kgs, compared to only 17 (28.33 percent) neonates who did not show much improvement in birth weight despite hospital management [22].

In our study, 18 neonates in the Sildenafil citrate group, and 20 neonates in the Nitroglycerine were admitted to the neonatal intensive care unit (NICU) and stay more than 15 days due to either low birth weight at the time of delivery or presence of other neonatal complications such as neonatal sepsis in 5 patients, respiratory distress syndrome in 23 patients, convulsion in 3 patients, intraventricular hemorrhage in one patient. The overall mortality was shown in nine cases (9%). In terms of complications, there was no significant difference between the two groups studied.

In the Trapani et al. study, only 16 neonates out of a total of 60 cases of IUGR neonates suffered from neonatal complications. The majority of them were caused by either birth asphyxia or neonatal sepsis. Five (9%) babies had birth asphyxia with a low APGAR score and were admitted to the NICU for treatment. Furthermore, 6 (10%) had neonatal sepsis in the immediate post-natal period. Only two (3.33 percent) of the neonates had MAS, while three (5.0 percent) had early neonatal jaundice and were treated accordingly. There were no neonatal deaths. [9].

The APGAR score reflects the newborn's hypoxemic status during the stress of labor. It is a reliable predictor of the fetus's placental reserve, particularly in IUGR pregnancies (30). The current study , in the Sildenafil group, In the Nitroglycerin group, Only 11 women had a 1 minute APGAR score of 7 and 7 women had a 5 minute APGAR score of 7. In terms of, there were no statistically significant differences between the two groups. the number of cases with a 1 minute APGAR score and those with a 5 minute APGAR score7. In the current study, all baseline Doppler US studied indices were similar in women in the Sildenafil citrate group compared to their levels in women in the Nitroglycerine group [(1.31 ±0.16 vs. 1.3 ± 0.09 for Umbilical artery PI), (1.68± 0.13 vs. 1.69 ±0.11 for MCA PI) and (1.3± 0.29 vs. 1.29 ±0.23 for uterine artery PI). After administration of therapy either Sildenafil citrate or Nitroglycerine, both umbilical artery PI and uterine artery PI decreased significantly (P ≤0.001). No change was observed in MCA-PI with the use of Sildenafil (P=0.676), but MCA increased significantly administration of Nitroglycerine (P<0.001).

Whereas mean arterial blood pressure was significantly higher in women given Sildenafil citrate (95.9 5.39) than in women given Nitroglycerine (91.36 3.7) (P0.001). In addition, both sildenafil (92.5 5.1) and Nitroglycerine (88.94 3.4) significantly reduced mean arterial blood pressure (P 0.001). Trapani Jr. et al. 35 singleton pregnancies with IUGR and abnormal uterine and umbilical artery Doppler waveforms were studied, and our

findings were confirmed. Before and after a transdermal Nitroglycerin patch (average dose 0.4 mg/h), oral Sildenafil citrate (50 mg), or placebo administration , maternal arterial blood pressure and Z-scores for the PI of the uterine, umbilical, and foetal middle cerebral arteries (MCA) were measured. The starting mean arterial blood pressure with Nitroglycerin was 1106.6. , then dropped to 986.1. (p-value 0.05). In addition, Sildenafil, it was initially 1087.1, then dropped to 925.6. (p-value 0.05). While the placebo had no discernible effects [9].

Furthermore, both Nitroglycerin and Sildenafil citrate reduced uterine artery PI significantly. Nitroglycerin and sildenafil citrate both showed a significant reduction in umbilical artery PI. When the Nitroglycerin and Sildenafil groups were compared, there was no difference in Doppler PI for the uterine and umbilical arteries. The placebo group showed no changes in Doppler velocimetry. In any of the groups, there was no significant change in MCA PI. The placebo group's uterine artery RI (p0.5) increased significantly, resulting in a higher mean gestational age at delivery in the treated group than in the placebo group. This lends credence to the study's findings. [9].

Furthermore, our findings agreed with those of the El-Bheirey et al.[13] study, which included 50 singleton pregnancies divided into two groups: Sildenafil citrate and Nitroglycerin. On the day after receiving medication, they discovered a statistically significant (7 percent) reduction in mean arterial blood pressure (MAP) in the Sildenafil group., and a 9 percent reduction in MAP in the Sildenafil group on the 21st day compared to before medication in the Sildenafil group. Furthermore, there was a statistically significant reduction (16%) in MAP on the day after receiving medication, and a statistically significant reduction (18%) in MAP on the 21st day compared to before medication in the Nitroglycerin group (23). Furthermore, the Doppler US revealed a significant reduction in umbilical artery RI and uterine artery RI in the two groups on the day after medication and the 21st day in the El-Bheirey et al.[13] study. There were no significant changes in MCA RI concern, nor was there a significant difference between the two groups. [23].

Some studies have found that Sildenafil has a positive effect on foetal growth. Mahmoud also reported a significant reduction in both uterine artery PI and umbilical artery PI with Sildenafil treatment in 50 women at high risk of developing IUGR and 50 others who had already been diagnosed with IUGR.

(EFW $\leq 10^{th}$ percentile). They also observed a significant reduction in maternal blood pressure with sildenafil use. There was an enhancement of restricted growth, as well as prevention of IUGR development in high-risk pregnancies, supporting not only the use of sildenafil citrate for the treatment of IUGR but also its use for IUGR prevention in high-risk pregnancies [21].

Also, a decrease in uterine artery PI and umbilical artery PI with the use of Sildenafil citrate has been shown previously in an in-vivo animal study by Stanley et al. [(32)], as well as some case reports by Panda et al. [23], and Lin et al. [24].

Going with our results, Dastjerdi et al. [25], El-Sayed et al. [26], and Premalatha et al.[27] showed that a significant decrease in the uterine and umbilical arteries pulsatility indices ingrowth restricted pregnancies treated with Sildenafil citrate.

In contrast, Samangaya et al.[28] concluded that using Sildenafil in women with established pre-eclampsia is not recommended because the women may have been too far along the pathophysiological process, such that improving uteroplacental blood flow had no effect on the release of circulating factors or established endothelial dysfunction.; however, the drug showed some effect on fetal growth [28].

Previous research with smaller sample sizes and more diverse enrollment criteria discovered that intravenous, sublingual, and transdermal nitroglycerine reduced uteroplacental vascular resistance, as in the study by Johal et al. [29].

Furthermore, the effect of nitroglycerine on severe pre-eclampsia pregnancies was investigated, and abnormal uterine and umbilical artery Doppler waveforms were documented. Trapani and his associates . [9], and Gupta et al [(41)] observed a significant reduction in the PI of the uterine arteries. No significant change in the PI of the middle cerebral artery was observed. All of these are similar results to the present study.

In pregnancies not complicated with pre-eclampsia, Kähler et al.[31] demonstrated that transdermal Nitroglycerine did not affect umbilical artery RI, but only affected mean uterine artery RI and nonplacental side uterine artery RI, both of which decreased significantly. The difference in their results from ours may be due to the use of RI to evaluate arteries while we used PI, also may be due to the less powerful study design and the smaller sample size they had (a prospective observational study including only 25 pregnant women at risk for preterm delivery) [24].

Previous studies by El-Bheirey et al.[13], 21.Mahmoud et al. [21] and Trapani et al. [9], After Nitroglycerine administration, The PI of the middle cerebral artery remained unchanged, indicating that the vascular tone of the foetal cerebral artery is not dependent on external nitric oxide supply. Our study's similar findings lend credence to this observation. With regard to side effects in the current study, Headache was the most common side-effect representing 20% (10 cases), and 42% (21 cases) in the Sildenafil group, the Nitroglycerine group respectively (P = 0.017). In addition, 22 patients suffered from visual disturbances after administration of therapy; 9 in the Sildenafil group and 13 in Nitroglycerine group II (P=0.334). Also, 5 (10%) patients in the Sildenafil group and 6 (12%) in the Nitroglycerine group had

facial flushing (P = 0.749). Furthermore, 3 cases in each studied group had dyspepsia. Moreover, there were 6 patients in the Sildenafil group and 10 patients in the Nitroglycerine group who had epigastric pain (P=0.275). Additionally, vomiting was detected in 5 (10%) women in the Sildenafil group and 7 (14%) in the Nitroglycerine group (P=0.538).

In et al. study, the headache was the most prominent side-effect in their study: 30 (43.3%) cases in the Nitroglycerine group and only 5 (16.6%) in the Sildenafil group (P = 0.024). Two (6.7%) patients in the Nitroglycerine group and 3 (10%) in the Sildenafil group had significant facial flushing (P = 0.0.23) [21].

The high prevalence of headaches in women who use Nitroglycerine is the main limiting factor for its clinical application in the context of placental vasculopathy, as Samangaya et al. have previously reported.[28], Mahmoud et al. [(31)], Johal et al.[29], and Gupta et al. [(40)]. It was, however, reassuring that the use of both drugs caused no severe hypotension or tachycardia in any patient. Headaches were tolerated and well-controlled using common analgesics and disappeared or decreased with adaptation to the medication.Overall, our results showed that Sildenafil has a hemodynamic action that is similar to that of Nitroglycerine in the treatment of cases of asymmetrical IUGR.

CONCLUSION

The current study concluded that using oral Sildenafil citrate and oral Nitroglycerin in the treatment of asymmetrical IUGR has a high significance, by reducing the uterine and umbilical arteries, a significant increase in placental blood flow was observed . The Doppler coefficients Because it has fewer side effects than Nitroglycerin, Sildenafil citrate may be preferred. The current study suggested that non-complicated IUGR cases be treated with sildenafil citrate and NTG.

Conflict of interest : none

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