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The Effect of Sildenafil on Intrauterine Growth Restriction (*IUGR*) of Fetus with Gestational Age above 28 Weeks and Neonatal Outcomes

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Abstract

Background

Intrauterine growth restriction (IUGR) is one of the main causes of mortality and morbidities of the perinatal period. This study aimed to investigate the therapeutic effects of sildenafil on Intrauterine Growth Restriction (IUGR) of fetus.

Materials and Methods: This study was a double-blinded clinical trial performed on 80 pregnant women with gestational age above 28 weeks and fetal weight below 10% percentile and AC below 3%. The patients were divided into two groups: the recipient of 25 mg of oral sildenafil daily (n=40) (made by Marham Darou in Tehran, Iran), and the group, receiving placebo (n=40). The two groups were evaluated weekly in terms of ultrasound factors such as fetal weight, AC, PI, and RI of the umbilical and cerebral arteries, and S / D of the umbilical artery.

Results: The mean age of the patients was 30.86 ± 5.77 years. Regarding MCA.PI, UA.PI, S / D, MCA.R and UA.RI indices, it was observed that these indices improved significantly in the intervention group (P <0.05). In the intervention group, after receiving the drug, the mean number of days to delivery was 12.05 days, and in the control group, after receiving placebo was 10.00 days (P = 0.001). The mean birth weight and score of Apgar minutes 1 and 5 in the intervention group was significantly higher than the control group (P <0.05).

Conclusion

Sildenafil can improve MCA.PI, UA.PI, S / D, MCA.R and UA.RI indices. Sildenafil increase the mean birth weight and score of Apgar minutes 1 and 5. Additionally, hospitalization in the NICU after taking sildenafil is shortened.

Key Words: Fetus, Gestational age, IUGR, Neonate**,** Sildenafil.

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1- INTRODUCTION

Intrauterine growth restriction *(*IUGR*)* is one of the major problems in developing countries such as Iran. IUGR is one of the main causes of mortality and morbidities of the perinatal period, which is caused by abnormal placental formation and placental blood flow and its prevalence in Asia accounts for 21% to 28%of cases (1). Severe IUGR is significantly related to adverse pregnancy consequences such as infant and maternal death, necrotizing enterocolitis, respiratory complications, disabilities, and other risks to the baby's life including obesity and hypertensive disease in the future (2-4). It seems that with the increase in the number of days the fetus is kept in the uterine, the survival rate increases linearly after delivery, so that for each day of stay in the uterine, the survival of the baby increases by 2% (5). On the other hand, delayed delivery also increases the chances of the fetus encountering intrauterine pregnancy products. In a normal pregnancy, trophoblasts invade the mother's spiral arteries, resulting in decreased resistance and increased placental vascular flow (6).

Effective treatment for this disorder is not known, and most cases of expected treatments include rest at home and work stoppages outside, and periodic evaluations of fetal health. Recent studies have shown that sildenafil increases uterine blood flow and vasodilatation (3). Trophoblasts produce nitric oxide in normal pregnancies, which is a vascular vasodilator. They also found that IUGR was less likely to secrete nitric oxide from the placenta during pregnancy. CGMP facilitates the production of nitric oxide (7). Sildenafil is a phosphodiesterase type 5 inhibitor (PDE5 inhibitor), which is responsible for eliminating CGMP, thereby increases CGMP and nitric oxide (8-10). The effect of sildenafil on the treatment of placental dysfunction in animals has been investigated and confirmed. In this study, we investigated the therapeutic effects of sildenafil to improve placental function through Doppler ultrasound in fetuses whose growth disorder has been proven before and after receiving the drug (11). It should be noted that in several recent studies, contradictory results have been reported (11-16). For example in the study by Sharp et al. (11), in a randomized clinical trial study, no difference was observed between the two groups in terms of time interval to delivery. Also, there was no difference between the two groups in terms of neonatal mortality and birth weight. Overall, the rate of delivery complications was not established between the two groups receiving sildenafil and placebo, and a recent study by Pels et al. on infant weight at birth as well as postpartum complications did not require re-admission (12).

2- MATERIALS AND METHODS

2-1. Study design and population

The present study was a clinical trial performed on pregnant women with gestational age above 28 weeks and fetal weight below 10% percentile and AC below 3% who had impaired Doppler arterial ultrasound referred to Akbar Abadi hospital from 18 December 2019 to 22 April 2020. The method of sampling was convenient.

2-2. Methods

After obtaining written consent, the patients were divided into two groups: the recipient of 25 mg of oral sildenafil daily (n=40) (made by Marham Darou in Tehran, Iran), and the group receiving placebo (n=40). Concealment was done in such a way that no one was aware of the allocation until the end of the study. Random allocation of the groups was performed using Excel software. The sildenafil group received 25 mg of oral sildenafil, and the control group received a

drug with the same shape and weight daily. The pregnant women and statistical analyzer were unaware of the allocated groups, and then this study was double-blinded. The two groups were evaluated weekly in terms of ultrasound factors such as fetal weight, AC, PI, and RI of the umbilical and cerebral arteries, and S / D of the umbilical artery. The present study was a double blind clinical trial in which the patient was unaware of the type of intervention, and the ultrasound specialist did not know which patient was in which group. Assessments continued until delivery, and the age of birth and weight at birth and the baby's 1 and 5 minute Apgar and the need for hospitalization at the NICU were assessed. Inclusion criteria were 1) pregnancy with gestational age above 28 weeks. 2) Occurrence of IUGR in fetal weight below 10% percentiles and AC less than 3%. 3) Age over 19 years and under 45 years, and 4) Ultrasound indicating fetal vascular Doppler disorder. Exclusion criteria were 1) Patients with unknown gestational age, 2) Having specific fetal anomalies, 3) Taking vasodilator drugs, 4) Multiple pregnancy, and 5) Smoking or alcohol use drugs pregnancy. Apgar score was calculated by the following (**Figure.1**).

SCORE	0 points	1 point	2 points
Appearance - Skin colour	Cyanotic/ Pale all over	Peripheral cyanosis only	Pink
Pulse (Heart rate)	0	<100	100-140
Grimace - Reflex irritability)	No response to stimulation	Grimace (facial movement)/ weak cry when stimulated	Cry when stimulated
Activity - Tone	Floppy	Some flexion	Well flexed and resisting extension
Respiration	Apnoeic	Slow, irregular breathing	Strong cry

Fig.1: Calculation of the Apgar score in newborns.

According to the study by Maged et al. (16), the sample size in this study using the following formula and considering 5% alpha and 90% power was 40 people in each group.

$$n=\frac{(Z_{(1-\alpha/2)}+Z_{(1-\beta)})^2(sd_1^2+sd_2^2)}{d^2}$$

2-3. Ethical consideration

Human rights were respected in accordance with the Helsinki Declaration 1975, as revised in 1983. The informed consent was taken from the patients. Ethics committee of Iran University of Medical Science approved the study (Ethical code: IR.IUMS.FMD. REC.1398.442).

2-4. Statistical analysis

Qualitative data is presented as a percentage and frequency and quantitative data is presented as Mean ± standard deviation (SD). Kolmogorov Smirnov test was used to check normality. If the data distribution was normal, independent t-test was used and if the data distribution was abnormal, the Man-Whitney test was used to compare the means. Also, to test the relationship between qualitative variables,

Chi-square test was used. P-value less than 0.05 was considered statistically significant. All data were analyzed using SPSS software (version 21.0).

3- RESULTS

The mean age of the patients was 30.86 ± 5.77 years. Patients were divided into control and intervention groups. Patients in the two groups were evaluated in terms of baseline characteristics and the results showed that the two groups of control and intervention were not significantly different in terms of demographic characteristics of pre-intervention indexes (P> 0.05). **Table.1** shows the demographic characteristics of the evaluated indexes of the two control and intervention groups.

Table-1: Demographic characteristics of the evaluated indexes of the two control and intervention groups before intervention, n=80.

Variables		Group		P- value
		Control (n=40)	Intervention (n=40)	
Age (Mean± SD)		29.85±5.86	31.88±5.57	0.118
(Mean± SD) Gestational age		238.25±5.47	238.70±5.95	0.726
EFW (Mean± SD)		1985.13±156.47	2005.75±150.26	0.549
PAPPA (Mean± SD)		0.48±0.28	0.47±0.32	0.22
MCA.PI	Abnormal	40(100)	40(100)	*
N (%)	Normal	0(0)	0(0)	
UA.PI	Abnormal	37(92)	38(95)	1.000
N (%)	Normal	3 (7.5)	2(5)	
S/D	Abnormal	39(97.5)	40(100)	1.000
N (%)	Normal	1(2.5)	0(0)	
MCA.RI	Abnormal	40(100)	40(100)	*
N (%)	Normal	0(0)	0(0)	
UA.RI	Abnormal	38(95)	39(97.5)	1.000

*No statistics are computed because variable distribution is a constant. SD: Standard deviation, MCA PI: Middle cerebral artery pulsatility index, RI: Resistive index, UA: Umbilical arterial, S/D: systolic/diastolic ratio.

After allocating the intervention, the evaluated indexes related to the mother were analyzed in two groups of control and intervention. The results showed that the rate of cesarean section in the two groups was not statistically significant (P = 0.256). Regarding MCA.PI, UA.PI, S / D, MCA.R and UA.RI indices, it was observed that these indices improved significantly in the intervention group (P<0.05). Also, the abdominal waist circumference above 10% in the intervention group was significantly higher than the control group (P <0.001). In the intervention group, after receiving the drug, the mean number of days to delivery was 12.05 days, and in the control group, after receiving placebo was 10.00 days (P=0.001) (**Table.2**).

Table-2: Evaluation of maternal indexes in two groups of control and intervention after intervention, n=80.

Variables		Group		P- value
		Control (n=40)	Intervention (n=40)	
MCA PI	Abnormal	34(85)	24(60)	0.012
N (%)	Normal	6(15)	16(40)	
UA.PI	Abnormal	33(82.5)	23(57.5)	0.015
N (%)	Normal	7 (17.5)	17(42.5)	
S/D	Abnormal	29(72.5)	17(42.5)	0.007
N (%)	Normal	11(27.5)	23(57.5)	
MCA RI	Abnormal	33(82.5)	24(60)	0.026
N (%)	Normal	7(17.5)	16(40)	
UA RI	Abnormal	32(80)	21(52.5)	0.009
N (%)	Normal	8(20)	19(47.5)	
Waist circumference	Abnormal	23(57.5)	34(85)	<0.001
above 10%	Normal	17(42.5)	6(15)	
Caesarean section	Abnormal	21(52.5)	26(65)	0.256
	Normal	19(47.5)	26(35)	
(Mean ± SD) Days to delivery		12.05±8.10	10.00±4.86	0.001

SD: Standard deviation, MCA PI: Middle cerebral artery pulsatility index, RI: Resistive index, UA: Umbilical arterial, S/D: systolic/diastolic ratio.

The infant-related indices were examined in two control and intervention groups. The results showed that the mean birth weight in the intervention group was significantly higher than the control group. (P = 0.036). Also, the mean score of Apgar minutes 1 and 5 was significantly higher in the intervention group, and this difference was statistically significant (P <0.05). In terms of hospitalization in the NICU in the intervention group, 10 cases (25%) were hospitalized in the NICU and in the control group 19 cases (47.5%) were admitted in the NICU (P = 0.036) (**Table.3**).

Table-3: Evaluation of infant-related indices in the two groups of control and intervention, n=80.

Variables		Group		P-value
		Control (n=40)	Intervention (n=40)	
Weight at birth (Mean± SD)		2224.00±150.05	2309.25±203.76	0.036
(Mean± SD) Apgar 1		7.65±0.77	8.05±0.84	0.030
Apgar 5 (Mean± SD)		9.43±0.59	9.68±0.47	0.041
Hospitalization in NICU	No (%)	21(52.5)	30(75)	0.036
	Yes (%)	19(47.5)	10(25)	

SD: Standard deviation, NICU: Neonatal intensive care unit.

4- DISCUSSION

Due to the severe outcomes of IUGR such as mortality and morbidities of the perinatal period, we investigated the therapeutic effects of sildenafil to improve placental function. In summary our results showed that the two groups of placebo and sildenafil were not significantly different in terms of demographic characteristics before intervention. The rate of cesarean section in the two groups was not statistically significant. Regarding MCA.PI, UA.PI, S/D, MCA.R and UA.RI indices, it was observed that these indices improved significantly in the intervention group. Also, the abdominal waist circumference above 10% in the sildenafil

group was significantly higher than the control group. In the sildenafil group, the mean number of days to delivery was 12.05 days, and in the control group, after receiving placebo was 10.00 days. The mean birth weight and score of Apgar minutes 1 and 5 in the sildenafil group was significantly higher than the control group. Regarding hospitalization in the NICU in the sildenafil group, 10 cases (25%) were hospitalized in the NICU and in the placebo group, 19 cases (47.5%) were admitted in the NICU. In a study entitled "the effect of sildenafil on possible IUGR pregnancies", found that the sildenafil group had 63% of mothers of infants with a weight above 10% and in the control group had only 20% of infants weighing more than 10% .The mean birth weight in the sildenafil group was 2,594 g and in the control group was 2,200 g.

The AC rate was improved by 70% in the sildenafil group, which was higher than the control group (34%) (8). In the comparative effects of nitroglycerin trans-dermal and sildenafil on improving IUGR, the results showed a significant reduction in uterine artery resistance in both nitroglycerin groups (21.3%) and sildenafil (20.2%) (9). Sildenafil reduces the resistance of uterine arteries and weight gain at birth (10). Also, AC accounted for more than 10% after receiving sildenafil in 66% of cases and aspirin in 58% of cases versus control in 38% of cases (9). In a study by Groom et al., First-born IUGR women entered the study at gestational age of 22 to 29 weeks. Patients were randomly treated with sildenafil citrate (25 mg) or placebo three times a day until week 32. First, sildenafil had no effect on fertility or fetal growth rate (52.5% vs. 68% in the placebo group). However, the use of sildenafil in the uterine artery was reduced after 48 hours of treatment by reducing the pulsatility index. The live birth rate in Sildenafil and placebo groups was 88.9% and 79.7%, respectively, hospital discharge with healthy infants was 66.7% and 55.9%, respectively, and pre-eclampsia rate was17.7% and 25.5%, which did not differ between the two groups (13). In a study by Pels et al., 360 pregnant women with severe IUGR entered the study and were treated with 25 mg sildenafil or placebo three times a day. In this study, there was no significant difference in any of the early results including PI of the placental artery, infant mortality rate, weight gain of the infant at birth and also the incidence of postpartum complications (12). Study by Pels et al. revealed contrary results compared to the results of our study because our results were approved the therapeutic effect of sildenafil on intrauterine growth restriction after intervention.

Von Dadelszen et al. performed a study on sildenafil citrate therapy for severe early-onset intrauterine growth restriction and showed that Sildenafil may provide more chance to improve perinatal outcomes of women with severe IUGR (14). In a small-randomized controlled trial to determine whether Sildenafil might prolong pregnancy in women with pre-eclampsia, 35 women developed pre-eclampsia with gestational age of 24–34 weeks were studied. Sildenafil dose gradually increased from 20 mg to 80 mg three times daily. There was no difference in terms of time to delivery between the two groups (15). Maged et al. in 2018 showed the same results (16).

Albeit in a study entitled" Sildenafil in pregnancy: a systematic review of maternal tolerance and obstetric and perinatal outcomes" done by Dunn et al., some complications were reported for Sildenafil such as headache followed by visual disturbance and gastrointestinal tract symptoms. Then it is suggested to increase the dose of Sildenafil slowly and step by step (17). In a study by Sharp et al., a randomized clinical trial was carried out on 135 women in two groups with

gestational age below 26 weeks and above 26 weeks randomly treated with sildenafil and placebo. In this study, first, there was no difference between the two groups in terms of time to delivery. In addition, there was no difference between the two groups regarding neonatal mortality and birth weight. Overall, regarding complications, there were no difference between the two groups receiving sildenafil and placebo (11). However, our results were not consistent with the study by Sharp et al. that is why we reported the higher mean weight at birth and time to delivery. They had subgroup analysis, it can affect the results, and the effect can be underestimated. Chen et al in a meta-analysis compared the effect of L-arginine and sildenafil citrate on intrauterine growth restriction and declared that L-arginine increases the weight at birth and gestational age (18).

These results were consistent with our results and some controversial results among the reported studies indicate the need to further studies with large samples as a prospective cohort studies (19-21). In a study by Kashanian et al., entitled "Comparison between two doses of betamethasone administration with 12 hours vs. 24 hours intervals on prevention of respiratory distress syndrome", the authors concluded that 12 hours interval betamethasone therapy can be considered as a treatment for preterm labour to accelerate the lung maturity (22). To prevent the probability complication, Javanmanesh and Eshraghi showed that recto-vaginal GBS culture screening in Iranian urban pregnant women regarding neonatal complication (23).

4-1. Study Limitations

One of the main limitations in this study was small sample size but considering that this study was interventional study, this limitation can be ignored. Follow-up of the patients were sophisticated and needed ore attempt to achieve the outcomes.

5- CONCLUSION

Sildenafil can improve MCA.PI, UA.PI, S / D, MCA.R and UA.RI indices in women who had *IUGR* with shorter hospitalization in the NICU. The mean number of days to delivery can be delayed by taking sildenafil. Sildenafil increase the mean birth weight and score of Apgar minutes 1 and 5. Therefore, sildenafil is suggested as a therapeutic drug in women with IUGR.

6- ABBREVIATIONS

IUGR: intrauterine growth restriction

CGMP: cyclic guanosine monophosphate

PDE inhibitor: phosphodiesterase inhibitors

PI: pulsatile index

RI: resistance index

MCA: middle cerebral artery

UA: umbilical artery

S/D: systole/diastole

AC: abdominal circumference.

7- AUTHOR CONTRIBUTIONS

NE and MM designed the study, observed accuracy and validity of the study. ME participated in the data collection. FK and NE supervised the project and wrote the paper. All authors edited and revised the final manuscript and accepted its publication.

8- CONFLICT OF INTEREST: None.

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