Al-Azhar International Medical Journal

Volume 2 | Issue 9 Article 6

9-1-2021

Sildenafil Versus Aspirin with Intrauterine Growth Restriction

ahmed hussein
Department of obstetrics and gynecology,Faculty of medicine,Al-Azhar university,Cairo,Egypt,
ahmedrajeh18@yahoo.com

Fahd Mohamed
Obstetrics and gynaecology department, Faculty of medicine, Al-Azhar university,
fahdelomda@yahoo.com

ahmed taha
Obstetrics and gynecology, Faculty of medicine, Al-Azhar university, dr.taha17@yahoo.com

Hisham Ali
Pediatrics and neonatology, Faculty of medicine, Al-Azhar university, drhishaly@yahoo.com

How to Cite This Article

hussein, ahmed; Mohamed, Fahd; taha, ahmed; and Ali, Hisham (2021) "Sildenafil Versus Aspirin with Intrauterine Growth Restriction," *Al-Azhar International Medical Journal*: Vol. 2: Iss. 9, Article 6.
DOI: https://doi.org/10.21608/aimj.2021.85294.1526

OPEN AIMJ ORIGINAL ARTICLE

Obstetrics and Gynecology

Sildenafil Versus Aspirin with Intrauterine Growth Restriction

Ahmed Rajeh Hussein Ali[1,*] M.B.B.CH, Fahd Abd El Aal Al Omd [2] MD, Fahd Abd El Aal Al Omda[2] MD and Hisham Ahmed Mohammed Ali[3] MD.

Corresponding Author:
Ahmed Rajeh Hussein Ali
ahmedrajeh18@yahoo.com

Received *for publication July 15, 2021;* ***Accepted*** *September 16, 2021;* ***Published online*** *September 16, 2021.*

doi: 10.21608/aimj.2021.85294.1526

[1]Risedent of Obstetrics and Gynecology Department, Samalot general Hospital, Egypt.

[2]Obstetrics and Gynecology Department, Faculty of Medicine, Al-Azhar University Cairo, Egypt.
[3]Pediatrics Department, Faculty of Medicine, Al-Azhar University Cairo, Egypt.

ABSTRACT

Background: Fetus growing restriction (FGR) or intra-uterine growth restriction (IUGR) is definite nowadays as the fetal failures of growing possibility and represented as one of the most discussed problems in obstetrics, which was in nonstop searching for improvements in term of definitions, classifications, diagnosing and managements.

Aim of the work: How to assess the consequence of Sildenafil and Aspirin in Doppler indices and the neonatal outcome in cases with placental non-sufficiency and FGR.

Patients and methods: this work was a randomized clinical study performed at Samalot General Hospital from March 2020 till September 2020.

Results: There is significant change among studied groups regarding RI and significant change among studied groups regarding PI of uterine artery whereas there is nonsignificant change among 2 groups regarding RI or PI middle cerebral artery. In Group-A there were 1(2.2%) with Failure of intervention. In Group-B there were 3(6.7%) with Failure of intervention. There is nonsignificant change among study groups.

Conclusion: from the findings of our work, we reported that sildenafil has advantageous impacts in the treating plan of growing limited fetus rather than aspirin alone with improvement of fetus growing parameters.

Keywords: *Aspirin; Neonatal Outcome; Obstetrics; Sildenafil.*

Disclosure: *The authors have no financial interest to declare in relation to the content of this article. The Article Processing Charge was paid for by the authors.*
Authorship: *All authors have a substantial contribution to the article.*

INTRODUCTION

Fetus growing restriction (FGR) or intra-uterine growth restriction (IUGR) is definite nowadays as the fetal failures of growing possibility and represented as one of the most discussed problems in obstetrics, which was in nonstop searching for improvements in term of definitions, classifications, diagnosing and managements.[1]

IUGR is the mutual end consequence of placental, maternal, fetal, or genetic influences, and IUGR may as well produce because of combinations of any of these reasons. Several maternal influences like mother age, interpregnancy period (<6-mths or ≥120-mths), mother health, behaviors, and motherly infections influence the fetus growing and are accountable for producing IUGR.[2]

FGR-fetuses have significantly higher risk of intra-uterine fetal demises, neonatal death, and short- and long-term complication.[3]

The strategies of the Royal college of Obstetrics and Gynaecology (RCOG) indorse the managements of these IUGR-fetuses counting imaging and birth procedures. Females with an FGR-fetus amid 24^{+0} and 35^{+6}-wks of pregnancy must have a single course of pregnancy corticoids, when birth is under consideration. Umbilical artery (UA) Doppler should be the principal FGR-surveillance instrument, as this has revealed to decrease perinatal morbidities and mortalities in high-risky people. Repeated surveillance of repeated Doppler was depending on the preceding Doppler indices.[4]

Doppler assessment of uterine and umbilical arteries speed wave-forms as a technique of monitoring of high blood pressure and FGR as Uteroplacental blood flowing reductions in gestations that are complicated by high blood pressure and IUGRs.[5]

Medications growing the impact of NO can be potential therapeutical agents for IUGR. Sildenafil citrate acting by blockage of phosphodiesterase-5 inhibitors that break-down cGMP, subsequently, intermediating the vasodilator impacts of NO.[6]

A research studied the impact of Sildenafil-citrate on uteroplacental perfusions in FGR gestations and reported that Sildenafil 25-50 mg has been accompanying with significant alteration in the fetoplacental Doppler Flowing Veloci-metry waveform, in comparison with control group. This hypothesis stems from the comparations among the patho-physiology accompanying with preeclampsia and FGR because of relative placental hypoperfusions.[7]

IUGR is frequently linked with preeclampsia, but it may as well happen with no any motherly hypertensions or proteinuria. New patho-physiological investigations have concentrating on preeclampsia, which is progressively recognized to be an early disorder of the trophoblast considered by mal-adaptation of the spiral artery, endothelial injuries, and minor thrombosis .[8]

Grounded on this supposition, some researches have established that low dosage aspirin may correct the intra-vascular non-balance among PGI2 and TXA2, consequently avoiding or delaying the pathogenesis of the disorder .[9]

Histologically, IUGR displays a similar faulty placentation as preeclampsia. Therefore, if low dosage aspirin prophylaxis against preeclampsia is operative it may avoid not only that disease but also some situations of IUGR by fluctuating the equilibrium to inhibitions of TXA2 synthesis and thus improve uteroplacental blood flowing .[10]

PATIENTS AND METHODS

ThThis work was a randomized clinical trial done at Samalot General Hospital from March 2020 till September 2020. Ninety cases with a singleton gestation, amid 24 and 34-weeks, with FGR and placental non-sufficiency, cases have separated into 2 groups: Group-A (45-cases): gestations impacted by FGR received Sildenafil (Silden® 25-mg tablet, manufactured by EIPICO, Inc, Cairo, Egypt) Group-B (45 patients): gestations influenced by FGR received Aspirin 75-mg (Aspocid® 75-mg tablet, manufactured by CID, Inc, Cairo, Egypt). With Inclusion criteria: Gravid females, singleton gestation, pregnancy aging from 24 to 34-weeks with, FGR, intact membrane, irregular UA Doppler Wave-forms, fetus abdomen perimeter at or less the 10th percentile, irregular fetus middle cerebral artery Doppler and nonsymmetric IUGR: Fetal mass is decreased out of percentage to extent and head perimeter, It happens late in gestation, throughout the phase of cellular hypertrophy, and is because of uteroplacental non-sufficiency. And Exclusion criteria was non-determined pregnancy ages, intra-uterine infections, high-risky for aneuploidy (e.g, motherly ages>40-yrs , noticed congenital fetal irregularities in the present or preceding gestations, maternal cardio-vascular morbidities (cardiac disease), using any vasodilator agent, maternal Blood clotting disorder ,liver and kidney disease, known allergy to Sildenafil or aspirin and symmetric-IUGR: The head circumferences, lengths and weights are all proportionally decreased for age of gestation, Because of either a congenital contagion or a genetic disease happening early in gestation, throughout the interval of early fetus cellular hyperplasia.

Methods:

All cases were exposed to the next:

Comprehensive individual, obstetric and medical history counting: Personal history including age, smoking and level of education, obstetric history including gravidity , parity, number of abortions , modes of delivery in previous pregnancies , first day of the previous normal menstrual interval and the pregnancy age , onset , duration and frequency of labor pains , urinary symptoms (dysurea , frequency , urgency) , vaginal discharge (color , itching). Medical history including Present or Past history of any chronic illnesses (renal, hypertensive, diabetics, hepatic, cardiac, …)

Examinations: Critical symptoms: Blood pressure, temperature, and pulse, mass, tall, BMI, abdominal examination for assessment of fundal level and fetal heart Sounds, abdominal palpation to notice uterine activities (period, frequency, and strength), evaluate fetus size and presentations and assessment of contraction done to diagnose threatened preterm birth(Contractions must be of four in 20 minutes or eight in 60 minutes each last 30 seconds or more with cervical changes (dilatation $\leq$ 3 cm, effacement $\leq$ 80%).

Assessment of fetal well-being: Pelvic ultrasound for assessment of amniotic fluids index and UA-Doppler, evaluation of estimated fetal weight. CTG - FHR patterns and indication of uterine activities.

Lab assessment: All investigations obtained according to standard protocol of PTL in our hospital including complete blood count, CRP and grouping , liver enzymes , kidney functions , random blood sugar , urine analysis and culture , high vaginal swap, calponin 1 serum level .

Interventions: In cases with FGR and irregular UA-Doppler, were arbitrarily allocated to two groups that will be treated with sildenafil as well Aspirin. This work compared the resistance-index (RI) and the pulsatility-index (PI) of the UA and the fetuses middle cerebral arteries, twice weekly after the introduction of 25-mg of sildenafil citrate (Silden® 25-mg tablet, manufactured by EIPICO, Inc, Cairo, Egypt) 8 hourly starting at diagnosing till birth vs. those who received Aspirin 75-mg (Aspocid® 75-mg tablet, manufactured by CID ,Inc, cairo , Egypt) two pills once daily starting at diagnosis until delivery. Using Diagnostic Ultrasound System manufactured by Shenzhen Mindray Bio-Medical Electronics Co., LTD. Model: Z5 SN: 6J-31000044.

Primary outcome: The impact of Sildenafil and Aspirin on Doppler velocity indices of the umbilical arteries and the fetus middle cerebral arteries in cases with placental non-sufficiency and FGR

Secondary outcome: Maternal: Possible side effects of sildenafil including common effects: headaches, flushing, nasal congestion, dyspepsia, vision blurring, photophobia, cyanopsia (blue vision) ,dizziness , postural hypotension and urinary tract infection. Other minor effects: palpitation, diarrhea, vomiting, sweating, backache and arthralgia. Rare serious effects: loss of peripheral vision, allergic

reactions, sudden hearing loss and chest pain. Possible maternal complications: Increased risk of hypertension, diabetes mellitus. Possible side effects of Aspirin including: Stomach upset heartburn, nausea and vomiting and Rare serious side effects including easy brusing/bleeding, dizziness, ringing in the ear, dark urine. Possible maternal complications: Increase risk of peptic ulcer. Fetal: Decreased fetal kicks, abnormal CTG changes and cardiac dysfunctions consequences in irregular venous flowing speed shapes counting opposite flowing in the ductus venosus throughout atrial contractions and pulsations in the umbilical veins. Neonatal Pregnancy age assessment at delivery by the ballard score, neonatal birth weight, Length and head circumference, neonatal complication rate (RDS ,Neonatal anemia, Neonatal blood transfusions) and neonatal ICU rate of admittance (Neonatal asphyxia or mechanical ventilation)

Statistical analysis: Analyzing of the collected performed via SPSS-20 (SPSS Inc., Chicago, IL, USA). Quantitative variables have been presented as mean and standard deviation. Qualitative variables have been presented in terms of numbers and percentage. So as to match parametric quantitative parameters among 2 groups, Student t testing has been used.

RESULTS

Demographic data	Group-A (n =45)		Group-B (n =45)		Test of Sig.	p
	No.	%	No.	%		
Age (years) < 30 ≥ 30	 27 18	 60.0 40.0	 27 18	 60.0 40.0	χ^2= 0.000	1.000
Min. – Max. Mean ± SD. Median (IQR)	23.0 – 35.0 28.44 ± 4.0 28.0 (25.0 – 32.0)		23.0 – 35.0 28.78 ± 3.38 29.0 (26.0 – 31.0)		t= 0.427	0.670
BMI Overweight 25- <30 Obese ≥ 30	 13 32	 28.9 71.1	 20 25	 44.4 55.6	χ^2= 2.344	0.126
Min. – Max. Mean ± SD. Median (IQR)	27.10 – 35.0 31.49 ± 2.56 32.10 (28.60 – 33.90)		27.20 – 34.80 30.44 ± 2.60 30.70 (27.90 – 32.80)		t= 1.927	0.057
Residence Rural Urban	 31 14	 68.9 31.1	 32 13	 71.1 28.9	χ^2= 0.053	0.818
Socioeconomic State Low Medium	 33 12	 73.3 26.7	 35 10	 77.8 22.2	χ^2= 0.241	0.624

χ2: Chi square testing t: Student t-testing U: Mann Whitney testing

p: p-value for comparison among the study groups

Group-A: patient's pregnancies affected by FGR being treated with Sildenafil

Group-B: patient's pregnancies affected by FGR being treated with Aspirin 75-mg

Table 1: Comparing among the studied groups regarding demographic data.

In Group-A there were 27(60%) less than 30 years old, 32(71.1%) obese, 31(68.9%) rural. 33(73.3%) with low socioeconomic status. In Group-B there were 27(60%) less than 30 years old, the mean age 28.78(±3.38 SD) with range (23-35), 25(55.6%) obese, 32(71.1%) rural. 35(77.8%) with low socioeconomic status. There is nonsignificant change among studied groups. Table (1)

Fetal Measurements	Group-A (n =45)	Group-B (n =45)	t	p
Abdominal circumference Min. – Max. Mean ± SD. Median (IQR)	 17.3-20.9 17.8±0.45 19.1(18.1-19.7)	 17.2-20.8 17.7±0.41 19.2(18.0-19.8)	0.324	0.731
Biparietal diameter Min. – Max. Mean ± SD. Median (IQR)	 5.0 – 7.0 5.82 ± 0.61 5.90 (5.20 – 6.20)	 5.0 – 7.0 5.90 ± 0.66 5.80 (5.30 – 6.40)	0.596	0.553
Femur length Min. – Max. Mean ± SD. Median (IQR)	 3.20 – 6.70 4.81 ± 0.96 4.90 (4.10 – 5.50)	 3.40 – 6.80 4.77 ± 0.89 4.80 (4.10 – 5.40)	0.194	0.847
Estimated fetal weight Min. – Max. Mean ± SD. Median (IQR)	 1117.0 – 1276.0 1194.5 ± 49.43 1198.0(1147.0–1235.0)	 1114.0 – 1271.0 1190.5 ± 46.23 1198.0(1148.0–1225.0)	0.394	0.694
Estimated fetal weight at term	**Group-A (n =45)**	**Group-B (n =45)**	**t**	**p**
Min. – Max. Mean ± SD. Median (IQR)	1450.0 – 2450.0 1908.9 ± 298.2 1850.0(1600.0–2150.0)	1350.0 – 2050.0 1655.6 ± 192.0 1550.0(1500.0–1850.0)	4.792*	<0.001*

Table 2: Comparing among the study groups regarding fetal measurements and estimated fetal weight at term

There is nonsignificant change among the two groups regarding fetal measurements. There is highly significant change among 2 groups as regard estimated fetal weight at term. Table (2)

Mean UA before term	Group-A (n =45)	Group-B (n =45)	t	p
RI				
Min. – Max.	0.50 – 1.0	0.60 – 1.10		
Mean ± SD.	0.79 ± 0.11	0.88 ± 0.13	3.526*	0.001*
Median (IQR)	0.80 (0.70 – 0.90)	0.90 (0.80 – 1.0)		
PI				
Min. – Max.	0.80 – 1.40	1.10 – 1.70		
Mean ± SD.	1.14 ± 0.14	1.38 ± 0.19	6.827*	<0.001*
Median (IQR)	1.20 (1.10 – 1.20)	1.40 (1.20 – 1.50)		
Fetal middle cerebral artery	**Group-A (n =45)**	**Group-B (n =45)**	**t**	**p**
RI				
Min. – Max.	0.68 – 0.78	0.68 – 0.78		
Mean ± SD.	0.73 ± 0.03	0.74 ± 0.03	1.664	0.100
Median (IQR)	0.73 (0.71 – 0.75)	0.74 (0.72 – 0.76)		
PI				
Min. – Max.	1.20 – 1.83	1.20 – 1.84		
Mean ± SD.	1.55 ± 0.19	1.59 ± 0.20	0.941	0.349
Median (IQR)	1.61 (1.40 – 1.70)	1.64 (1.39 – 1.74)		

Table 3: Comparing among the study groups regarding mean UA before term and fetal middle cerebral artery

There is significant change among study groups regarding RI and significant change among studied groups regarding PI of uterine artery while there is nonsignificant change among 2 groups regarding RI or PI middle cerebral artery. Table (3)

	Group-A (n =45)		Group-B (n =45)		χ^2	^{FE}p
	No.	%	No.	%		
Failure of intervention						
No	44	97.8	42	93.3	1.047	0.616
Yes	1	2.2	3	6.7		
Babies admitted to NICU						
No	36	80.0	32	71.1	0.963	0.327
Yes	9	20.0	13	28.9		

Table 4: Comparing among the study groups regarding failure of intervention and Babies admitted to NICU

In Group-A there were 1(2.2%) with Failure of intervention. In Group-B there were 3(6.7%) with Failure of intervention. There is nonsignificant change among 2 groups. In Group-A there were 9(20%) Babies admitted to NICU. In Group-B there were 13(28.8%) Babies admitted to NICU. There is nonsignificant change among study groups. Table (4)

Birth weight	Group-A (n =45)	Group-B (n =45)	t	p
Min. – Max.	1560.0 – 2650.0	1370.0 – 2240.0		
Mean ± SD.	2007.3 ± 314.5	1754.7 ± 227.5	4.367*	<0.001*
Median (IQR)	2000.0(1740.0–2230.0)	1660.0(1610.0–1990.0)		
APGAR score	**Group-A (n =45)**	**Group-B (n =45)**	**t**	**p**
Min. – Max.	5.0 – 10.0	5.0 – 10.0		
Mean ± SD.	8.44 ± 1.32	8.16 ± 1.49	0.972	0.334
Median (IQR)	9.0 (8.0 – 9.0)	8.0 (8.0 – 9.0)		

Table 5: Comparing among the study groups regarding birth weights and APGAR score

There is high significant difference between 2 groups as regard birth weight while thre is nonsignificant change among the two groups regarding APGAR score. Table (5)

DISCUSSION

A case-control research has been made, consisted of 90 women with a singleton pregnancy, between 24-34 weeks, with FGR and placental non-sufficiency. Patients were recruited from Samalot General Hospital then arbitrarily allocated to 2 groups. Group-A (4-cases): gestations influenced by FGR recieved Sildenafil (Silden® 25-mg tablet, manufactured by EIPICO, Inc, Cairo, Egypt). Group-B (4-cases): gestations influenced by FGR recived Aspirin 75-mg (Aspocid® 75-mg tablet, manufactured by CID ,Inc ,cairo , Egypt). The period of the work ranged from 6 to 12-mths.

There is nonsignificant change among study groups as regard age, BMI, gravidity, parity and pregnancy age. In Group-A there were 27(60%) less than 30 years old, 18(40%) more than 30, the mean age 28.44(±4 SD) with range (23-35). In Group-B there were 27(60%) less than 30 years old, 18(40%) more than 30, the mean age 28.78(±3.38 SD) with range (23-35).

Our results were in agreement with study of SHALABY[11,] as they reported that there was nonsignificant change among both study groups in regard to maternal ages, pregnancy, parity and pregnancy age. The report involved 100-patients with fetal IUGR 50-patients in the sildenafil treatments Group and 50-patients in the heparin/low doses aspirin group.

Sildenafil citrate rises uterine blood flowing and potentiate estrogen persuaded vasodilatations. Intra-vaginal administrations of sildenafil in the achievement of in vitro fertilizations show no harmful impacts on mothers and fetuses. The natural killer cells activities and endometrial width have been significantly altered afterward vaginal sildenafil treatment so it may be an exciting treatment choice earlier to the conception in females with recurrent re-productive failures [12.]

The current work showed that there is nonsignificant change among study groups as regard Symphysis fundal height measurement. In Group-A the mean Estimated fetal weight 1194.5(±49.43 SD) with range (1117-1276), the mean Biparietal diameter 5.82(±0.61 SD) with range (5-7), the mean Femur length 4.81(± 0.96 SD) with range (3.2-6.7). In Group-B the mean Estimated fetal weight 1190.5(±46.23 SD) with range (1114-1271), the mean Biparietal diameter 5.9(±0.66 SD) with range (5-7), the mean Femur length 4.77(± 0.89 SD) with range (3.4-6.8). There is nonsignificant change among study groups.

Our findings were in agreement with Mousa et al., [13] as they reported that a nonsignificant change was found among the studied groups previous to the start of therapy in regard to fetal biometry (BPD, FL, AC and EFW) via US. When matching among the 2 groups after the therapy as regard the fetus biometry revealed that a nonsignificant change was found. Group-A n=40: (Sildenafil-group) & Group-B n=43: (Heparin/Aspirin-group).

Our results were in contrary with study of SHALABY, [11] as they showed a significant rise in fetus growing measurement afterward sildenafil citrate treatments (p-value=0.002) and this was agreement with that performed who concluded an improvements of sildenafil on fetus growing measures principally AC & EFW vs. no therapy.

Early-onsets of FGR at <32-wks pregnancy age is accompanying with considerable neonatal morbidities and mortalities. The reasons of FGR comprise fetal, maternal, and placental influences, in addition to the constitutional small fetuses. Pathological growing restrictions are frequently accompanying with anomalous UA and ductus venous Doppler investigations .[14]

This work revealed that there is significant change among 2 groups as regard RI and significant change among studied groups as regarding PI of UA. In Group-A the mean RI Fetal middle cerebral artery 0.73(± 0.03 SD) with range (0.68-0.78), the mean PI Fetal middle cerebral artery 1.55(± 0.19 SD) with range (1.2-1.83). In Group-B the mean RI 0.74(± 0.03 SD) with range (0.68-0.78), the mean PI 1.59(± 0.2 SD) with range (1.2-1.84). There is nonsignificant change among study groups.

Our findings were in agreement with Dastjerdi et al., [15] as they found that the sildenafil group fetuses showed a significant reduction in S/D ratios [0.60 (SD: 0.40) (95% CI: 0.37– 0.84), P-value<0.001] and PI (0.12 (SD: 0.15) (95% CI: 0.02– 0.22), P-value=0.019] for the UA and a significant rise in MCA PI [0.51 (SD: 0.60) (95% CI: 0.16–0.85), P-value=0.008]. They concluded that Doppler veloci-metry index records mirror reduced placental bed vascular resistances afterward sildenafil administrations.

Furthermore, Choudhary et al., [16] revealed that the UA diastolic flowing enhanced afterward 2-wks of treatment, with no brain-sparing imapct in MCA; but, the S/D ratio was greater than 3.

In another hands, Shehata et al., [17] demonstrated that umbilical and middle cerebral artery Doppler indices revealed significant change among groups afterward intakes of sildenafil. UA-PI reduced significantly (p-value = .001) whereas middle cerebral artery PI raised significantly in treatment group (p =.001).

Another important finding in the results of Mousa et al., [13] was the influence of sildenafil citrate on placental perfusions assessed via variations in UA-Doppler and middle cerebral arteries Doppler where significant differences in Doppler indices happened afterward therapy. This concluding result was in agreement with a report studied as well the impact of sildenafil citrate on uteroplacental perfusions in high-risky gestations patients performed by Marzieh et al., [18].

In the study in our hands, there is highly significant change among studied groups as regarding estimated fetal weight at term. There is nonsignificant change among study groups as regard failure of intervention. There is highly significant change among both groups regarding birth weight.

Our findings were in accordance with that of SHALABY, [11] as they proved a significant rise in assessed fetal weight afterward sildenafil citrate therapy (p=0.001).

These findings were consistent with Miller et al., [19] who found in an experimental animal study that sildenafil decreased flow of uterine blood and this was related with significant deteriorations in fetus wellbeing. They explained their findings by the action of sildenafil on maternal systemic circulation, altering it and resulting in flow of the blood steal from the utero-placental circulations to the systemic vascular circulation that lowered its resistance due to widespread systemic vasodilatation. This may be explained as there is wide cellular and tissue distributions of the PDE enzymes through the body and consequently absence of comparative specificity within the uteroplacental circulations. These findings of Miller et al., [19] in the animal study couldn't be confirmed in human.

Furthermore, Choudhary et al., [16] reported that US at 30-wks revealed an AFI of 7.5 and a fetus weight of one kg. The patients as well underwent a personal rise in perceptions of fetus movement. All drugs were sustained with every week measurements of fetus weight and AFI. Regularly at 31-wks, there was additional reduction in PI, and S/D ratio was less than 3, in umbilical as well as MCAs.

Ferreira et al., [20] revealed that a significant rise of 222.58-gm [27.75 - 417.41] was detected in the fetus weight at delivery of cases receiving sildenafil.

Researches have revealed that sildenafil. Aids in improving the uteroplacental flow of the blood and in order progresses the fetus weight via causation of vasodilatations of the intra-myometrial and intra-placental the vessels of the blood. Improved uteroplacental blood progresses the transfer of oxygen and other nutrients to fetuses, that cause better growing and developments. But, there is no conclusive therapy to progress the flow of blood to the fetuses [21].

However, Roberge et al., [22] reported that a significant decrease was found and a dose-respond influence for the avoidance of FGR (relative risk, 0.56; 95% confidence interval, 0.44–0.70; P-value< .001; R2, 100%; P-value= .044) with elevated doses of aspirin being accompanying with greater decrease of the 3 outcomes.

In the study of Bujold et al., [23], Low-doses aspirin started in early gestation is an effective technique of dropping the occurrence of pre-eclampsia and IUGR.

Sildenafil citrate, definite phosphodiesterase-5 inhibitors, was assumed as a possible treatment option to preserve placental functions and developing as a potential candidate for the IUGR therapy [24].

The current study showed that in Group-A the mean APGAR score 8.44(± 1.32 SD) with range (5-10). In Group-B the mean APGAR score 8.16(± 1.49 SD) with range (5-10). There is nonsignificant change among study groups. In Group-A there were 9(20%) Babies admitted to NICU. In Group-B there were 13(28.8%) Babies admitted to NICU. There is nonsignificant change among study groups.

Our findings were approved by report of Mousa et al., [25] as they reported that there were no changes in NICU admissions, survivals, early neonatal mortality or neonatal deaths among the studied groups.

CONCLUSION

From the findings of our work, we reported that sildenafil has advantageous influences in the treatment option of fetal restricted growth rather than aspirin alone with improvement of fetus growing parameters.

REFERENCES

1. Izquierdo M., Aldecoa, V., Balcells C., Del Rey B., Iriondo M., & Iglesias I. Applying methods for postnatal growth assessment in the clinical setting: evaluation in a longitudinal cohort of very preterm infants. *Nutrients*. 2019; 11(11), 2772.
2. Sharma, D., Shastri, S., & Sharma, P. Intra-uterine growth restriction: antenatal and postnatal aspects. Clinical Medicine Insights: *Pediatrics*. 2016; 10, CMPed-S40070.
3. Malhotra, A., Allison, B. J., Castillo-Melendez, M., Jenkin, G., Polglase, G. R., & Miller, S. L. Neonatal morbidities of fetus growing restriction: pathophysiology and impact. *Frontiers in endocrinology*. 2019; 10, 55.
4. Martins, J. G., Biggio, J. R., Abuhamad, A., & Society for Maternal-Fetal Medicine (SMFM. Society for Maternal-Fetal Medicine Consult Series# 52: Diagnosis and management of fetus growing restriction :(Replaces Clinical Guideline Number 3, April 2012). *American journal of obstetrics and gynecology*. 2020; 223(4), B2-B17.
5. Aplin, J. D., Myers, J. E., Timms, K., & Westwood, M. Tracking placental development in health and disease. *Nature Reviews Endocrinology*. 2020; 16(9), 479-94.
6. Maged, M., Wageh, A., Shams, M., & Elmetwally, A. Use of sildenafil citrate in cases of intra-uterine growth restriction (IUGR); a prospective trial. *Taiwanese Journal of Obstetrics and Gynecology*,. 2018; 57(4), 483-6.
7. Leavey, K. M. Unsupervised Multi-Scale Analysis for the Identification of Placental Subtypes of Human Preeclampsia and Fetus growing Restriction (Doctoral dissertation, *University of Toronto (Canada))*, 2018.
8. Lane-Cordova, A. D., Khan, S. S., Grobman, W. A., Greenland, P., & Shah, S. J. Long-term cardiovascular risks associated with adverse pregnancy outcomes: JACC review topic of the week. *Journal of the American College of Cardiology*. 2019; 73(16), 2106-16.
9. Jain, K. K. Neuroprotection in Cerebrovascular Disease. *In The Handbook of Neuroprotection*. 2019; 175-280.
10. Dutta, S., Kumar, S., Hyett, J., & Salomon, C. Molecular targets of aspirin and prevention of preeclampsia and their potential association with circulating extracellular vesicles during pregnancy. *International journal of molecular sciences*. 2019; 20(18), 4370.
11. SHALABY, H. A. Sildenafil Citrate versus Aspirin/Heparin Combination for Fetus growing Restriction: A Randomized Clinical Trial. *Med. J. Cairo Univ.* 2017; 85(7): 2461-7.
12. Jerzak M, Kniotek M, Mrozek J, Górski A. Sildenafll increases successful pregnancies after recurrent miscarriage. *Fertil Steril*. 2008; 90:1848–53.
13. Mousa, A. A. A., Mohamed, M. A., Radwan, M. S., & Sholkamy, A. M. Effect of Sildenafil Citrate When Added to Low Molecular Weight Heparin and Small Dose Aspirin on Uteroplacental Perfusion in Cases of High-Risk Pregnancy. *The Egyptian Journal of Hospital Medicine.* 2019; 75(5), 2934-1.
14. Ganzevoort W, Alfirevic Z, von Dadelszen P, Kenny L, Papageorghiou A, van Wassenaer-Leemhuis A, et al. STRIDER: Sildenafil Therapy in Dismal prognosis Early-onset intra-uterine growth Restriction–a protocol for a systematic review with individual participant data and aggregate data meta-analysis and trial sequential analysis. *Syst Rev*. 2014; 3:23.
15. Dastjerdi MV, Hosseini S, Bayani L. Sildenafil citrate and uteroplacental perfusion in fetus growing restriction. *J Res Med Sci*. 2012; 17:632–6.
16. Choudhary, R., Desai, K., Parekh, H., & Ganla, K. Sildenafil citrate for the management of fetus growing restriction and oligohydramnios. *International journal of women's health*. 2016; 8, 367.

17. Shehata, N. A., Ali, H. A., Fahim, A. S., Katta, M. A., & Hussein, G. K. Addition of sildenafil citrate for treatment of severe intra-uterine growth restriction: a double blind randomized placebo controlled trial. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2020; 33(10), 1631-7.

18. Marzieh VD, Sayedehafagh H and Leila B. Sildenafil citrate and uteroplacental perfusion in fetus growing restriction. *J Res Med Sci*. 2012; 17 (7): 632-6.

19. Miller SL, Loose JM, Jenkin G, Wallace EM. The effects of sildenafil citrate (Viagra) on uterine blood flow and well-being in the intra-uterine growth-restricted fetus. *Am J Obstet Gynecology*. 2009; 200(102):e1–7.

20. Ferreira, R. D. D. S., Negrini, R., Bernardo, W. M., Simões, R., & Piato, S. The effects of sildenafil in maternal and fetal outcomes in pregnancy: A systematic review and meta-analysis. *PloS one*. 2019; 14(7), e0219732.

21. Wareing M, Myers JE, O'Hara M, Baker PN. Sildenafil citrate (Viagra) enhances vasodilatation in fetus growing restriction. *J Clin Endocrinol Metab*. 2005; 90(5):2550-5.

22. Roberge, S., Nicolaides, K., Demers, S., Hyett, J., Chaillet, N., & Bujold, E. The role of aspirin dose on the prevention of preeclampsia and fetus growing restriction: systematic review and meta-analysis. *American journal of obstetrics and gynecology*. 2017; 216(2), 110-20.

23. Bujold, E., Roberge, S., Lacasse, Y., Bureau, M., Audibert, F., Marcoux, S., et al. Prevention of preeclampsia and intra-uterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstetrics & Gynecology*. 2010; 116(2), 402-14.

24. Villanueva-García D, Mota-Rojas D, Hernández-González R, Sánchez-Aparicio P, Alonso-Spilsbury M, Trujillo-Ortega ME, et al. A systematic review of experimental and clinical studies of sildenafil citrate for intra-uterine growth restriction and pre-term labour. *J Obstet Gynaecol*. 2007; 27(3):255-9.

25. Mousa, A. A. A., Mohamed, M. A., Radwan, M. S., & Sholkamy, A. M. Effect of Sildenafil Citrate When Added to Low Molecular Weight Heparin and Small Dose Aspirin on Uteroplacental Perfusion in Cases of High-Risk Pregnancy. *The Egyptian Journal of Hospital Medicine*. 2019; 75(5), 2934-41.