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Tadalafil Effect on Impedance to Flow in the Umiblical and Fetal Middle Cerebral Arteries in Pregnancies at High Risk for Fetal Growth Restriction

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Abstract

Background: Fetal growth restriction (FGR) is a common-complication of pregnancy that is associatedwith a variety of adverse perinatal outcomes. Tadalafil is a selective PDE5 inhibitor with a longer half-life and a more rapid onset of action compared with sildenafil. Tadalafil treatment was feasible in pregnant women showing FGR.

Aim of Study: This study aims to evaluate tadalafil as a prophylaxis to pregnancies at high risk for fetal growth restriction.

Patients and Methods: This study was carried out on 30 pregnant women attending Emergency Unit of Obstetrics and Gynecology Department, Zagazig University Hospitals. This group of patients was selected according to both present and past medical disorders and past obstetric history.

Results: Our results showed statistically significant differences in umbilical artery Doppler indices before, two hours and six hours following tadalafil therapy in the studied patients ($p<.05$). Also, there were statistically significant differences in middle cerebral artery Doppler indices before, two hours and six hours following tadalafil therapy in the studied patients ($p<.05$).

Conclusion: Tadalafil treatment may offer a promising therapy for fetal growth restriction with placental insufficiency.

Key Words: *Tadalafil – Fetal growth restriction – Doppler ultrasound – High risk pregnancy.*

Introduction

FETAL growth restriction (FGR) is a common complication of pregnancy that is associated with a variety of adverse perinatal outcomes **[1]**.

The etiology of FGR can be broadly categorized into maternal, fetal, and placental. Although the primary pathophysiologic mechanisms underlying these conditions are different, they often have the same final common pathway; suboptimal uteroplacental perfusion and fetal nutrition **[2]**.

Although the main indication when treating FGR is to consider the appropriate termination of the pregnancy, fetal prematurity depending on gestational age (GA) is a serious problem. A fetus with IUGR may be born small for gestational age (SGA) or appropriate for gestational age (AGA) according to population reference charts **[3]**.

There is also no proven fetal therapy to reverse or ameliorate established FGR. To prevent FGR, nutritional and dietary supplementation, bed rest, and aspirin therapy have been investigated **[1]**.

Placental perfusion is enhanced by nitric oxide (NO), which promotes vasodilatation of maternal vessels. cGMP, the second messenger of nitric oxide, is degraded by the phosphodiesterase enzyme. cGMP is inactivated mainly by phosphodiesterase (PDE), and PDE5 exists mainly in vascular smooth muscle cells **[4]**.

It is expected that PDE inhibitors could become therapeutic agents for FGR in light of the inhibitors' artery dilation function, as confirmed in studies of erectile dysfunction and pulmonary hypertension **[5]**.

Sildenafil citrate is an inhibitor of phosphodiesterase type 5 subsequently, it results in a rise in cGMP and consequent vasodilatation **[6]**.

Sildenafil citrate could be a potential therapeutic strategy to improve uteroplacental blood flow in pregnancies with fetal growth restriction (FGR); moreover, it has shown promising results in fetal growth restriction **[7]**.

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Dastjerdi et al., [8] determined whether the phosphodiesterase type 5 inhibitor, Sildenafil citrate, affects uteroplacental perfusion. They concluded that velocimetry index values reflect decreased placental bed vascular resistance after Sildenafil. Sildenafil citrate can improve fetoplacental perfusion in pregnancies complicated by intrauterine growth restriction. It could be a potential therapeutic strategy to improve uteroplacental blood flow in pregnancies with fetal growth restriction (FGR).

Tadalafil is another selective PDE5 inhibitor with a longer half-life and a more rapid onset of action compared with sildenafil [5]. Ladouceuret al., [9] showed the safety of tadalafil treatment for pregnant women.

Regarding the plasma concentration and the bioavailability of the drug, tadalafil is less susceptible to the intake of a high-fat meal and less influenced by sex compared with sildenafil [10].

Yoshikawa et al., [11] demonstrated that tadalafil treatment dilates thematernal blood sinuses in the placenta, which leads toincreased placental growth factor (PlGF) production and contributes to the facilitation of fetal growth.

Tadalafil treatment contributed to the facilitation of fetal growth via mechanisms associated with NO signaling, because the tadalafil treatment was initiated after blood spaces in the placenta were narrowed by the L-NAME treatment and an elevated urinary excretion of cGMP was observed [12].

Minakami et al., [13] showed that both fetal growth velocity from enrolment to birth and birth weight were significantly higher in the tadalafil group than in the conventional management group. Moreover, the prevalence of respiratory distress syndrome (RDS) was significantly lower in the tadalafil group compared with the conventional management group.

Kubo et al., [14] saw no severe adverse event was seen following the initiation of a daily tadalafil dose of 10mg, 20mg or 40mg except for one intrauterine fetal death case. The intrauterine fetal death was due to velamentous insertion of the umbilical cord. They concluded that tadalafil treatment was feasible in pregnant women showing FGR.

Although several other PDE5 inhibitors are available, such as sildenafil, tadalafil has a longer half-life than sildenafil (14-15h vs. 2-4h) and is consequently presumed to be more stable and effective [15].

Another benefit of the longer half-life of tadalafil is that one dose per day is sufficient, whereas sildenafil must be administered at least twice per day. Although PDE5 enzymes are widely distributed in blood vessels, tadalafil is particularly selective for PDE5 enzymes found in the reproductive organs [16]. Umekawa et al., [12] revealed that tadalafil administration prolonged gestation.

For the effective use of tadalafil for FGR, this study aims to evaluate tadalafil as a prophylaxis to pregnancies at high risk for fetal growth restriction.

Patients and Methods

Quasi experimental study was carried out at Emergency Unit of Obstetrics and Gynecology Department, Zagazig University Hospitals in Sharkia from January 2021 till October 2021.

We recruited thirty pregnant women at high risk for fetal growth restriction before administration of tadalafil, all of which were administered tadalafil (20mg/day, once-daily dosing).

The patients were recruited from Antenatal Outpatient Clinic.

Inclusion criteria:

1- Age group (24 : 35 years old).
2- Gestational age between 28-37 weeks.
3- Singleton pregnancy.
4- Pregnant at high risk for fetal growth restriction in Current pregnancy:
   a- Mild pre-eclampsia.
   b- Diabetes mellitus.
5- Previous pregnancy with:
   a- Small for gestational age.
   b- Stillbirth.
   c- Severe pre-eclampsia.
6- Normal non-stress test at time of admission.
8- Intact membranes.

Exclusion criteria:

1- Maternal anaemia, cardiovascular morbidity.
2- Users of any other vasodilator agents.
3- Fetal anomalies or chromosomal abnormalities.
4- Known intolerance to tadalafil.
5- Contraindication of tadalafil treatment due to renal disease, liver disease, uncontrolledarrhythmia, hypertension and hypotension, retinitis

pigmentosa, coagulation defect, active gastric and/or intestinal ulcer, or venous obstructive disease.

6- Reversed flow of the umbilical artery Doppler waveform needs for pregnancy interruption before completion of our study.

7- Severe pre-eclampsia or eclampsia.

Methods:

1- History taking for current pregnancy.

2- General examination: Blood pressure measurement, pulse, temperature and respiratory rate.

3- Obstetrical examination: Including abdominal and pelvic examinations.

4- Transabdominal obstetric Ultrasonography (U/S) was done for the pregnant women in a semi-recumbent position using Medisone, Accuivix v20 with a 3.5 MHz sector transducer for transabdominal ultrasound.

Umbilical artery Doppler:

All patients were placed in a semi recumbent position with a left lateral tilt, and then the uterine content was scanned to select an area of amniotic cavity with several loops of cord. Then using a pulsed wave Doppler on a free loop of cord, the characteristic sound and shape of the umbilical artery identified. When the screen showed at least 3 consecutive wave forms of similar height, the image was frozen and Doppler umbilical artery pulsatility index (UA-PI) was estimated. A minimum of 3 separate reading was averaged before the final value were obtained.

Middle cerebral artery Doppler:

Transverse view of the fetal brain was obtained at the level of the biparietal diameter. The transducer was then moved towards the base of the skull at the level of the lesser wing of the sphenoid bone. Using color flow imaging, the middle cerebral artery was seen as a major lateral branch of the circle of Willis, running anterolaterally at the borderline between the anterior and the middle cerebral fosse. The pulsed Doppler sample gate is then placed on the middle portion of this vessel to obtain flow velocity waveforms. When the screen showed at least 3 consecutive wave forms of similar height, the image was frozen and Doppler middle cerebral artery pulsatility index (MCA-PI) was estimated. A minimum of 3 separate reading was averaged before the final values were obtained care should be taken to apply minimal pressure to the maternal abdomen with the transducer, as fetal head compression is associated with alterations of intracranial arterial wave forms.

The pulsatility indices of the middle cerebral artery and umbilical artery were recorded. The patients with decreased middle cerebral artery PI and absent or reversed diastolic flow in umbilical artery were admitted for further evaluation and delivery.

Follow-up:

The patients have been followed-up until delivery and the effect of tadalafil on Doppler velocity indices of the umbilical arteries and fetal middle cerebral artery in patients were detected.

Outcome:

The outcome is defined as the improvement of uteroplacental perfusion measured by Doppler indices.

Statistical analysis:

Data were analyzed by Statistical Package of Social Science (SPSS), software version 24.0 (SPSS Inc., 2016).

Continuous data were presented as the Mean ± SD or Median (Range). Normality was checked by Shapiro-Wilk test. Categorical data were presented by the count and percentage.

The one-way repeated measure ANOVA is used to test for differences between groups when the dependent variable is normally distributed continuous variable.

Post hoc analysis with a Bonferroni adjustment is used for multiple comparisons following one-way repeated measure ANOVA to detect which occasion in particular differs from other occasions.

p-value <.05 indicates significant, p<.0 1 indicates highly significant difference, p<0.001 indicates very highly significant difference while, p≥.05 indicates non-significant difference.

Results

A 30 women with a singleton pregnancy, between 29-37 weeks were included in the study. Baseline characteristics of the studied patients were shown in Table (1).

Table (3) showed statistically significant differences in umbilical artery Doppler indices before, two hours and six hours following tadalafil therapy in the studied patients (p<.05).

Table (5) showed statistically significant differences in middle cerebral artery Doppler indices before, two hours and six hours following tadalafil therapy in the studied patients (p<.05).

Table (1): Baseline characteristics of the studied patients.

Variables	
Maternal age (years):	
Mean ± SD	30.5±3.5
Median (Range)	30 (26-35)
Gestational age (weeks):	
Mean ± SD	35.9±2.7
Median (Range)	36 (29-37)
Maternal parity, n, (%):	
Primipare	6 (20%)
Multipare	
2	6 (20%)
3	12 (40%)
4	3 (10%)
6	3 (10%)
Maternal risk, n, (%):	
Mild pre-eclampsia	
Yes	6 (20%)
No	24 (80%)
Diabetes mellitus:	
Yes	9 (30%)
No	21 (70%)
Intrauterine growth retardation:	
Yes	3 (10%)
No	27 (90)

Total number=30.

Table (2): Baseline data of umbilical artery Doppler indices of the studied patients.

Variables	
Umbilical artery systolic/diastolic ratio (UA S/D):	
Mean ± SD	3.3±0.50
Umbilical artery pulsatility index (UA PI):	
Mean ± SD	1.2±0.36
Umbilical artery resistance index (UA RI):	
Mean ± SD	0.79±0.2

Total number=30.

Table (3): Umbilical artery Doppler indices before, two hours and six hours following tadalafil therapy in the studied patients.

Variables	Pre-tadalafil n=30	Two hours-post tadalafil n=30	Six hours-post tadalafil n=30	Repeated measure ANOVA	*p*-value
UA Systolic/ diastolic ratio: Mean ± SD	3.3±0.49	3.0±0.39	2.7±0.22	F=23.8	<.001
UA pulsatility index: Mean ± SD	1.2±0.36	1.12±0.1	0.9±0.11	F=10.7	.001
UA resistance index: Mean ± SD	0.79±0.2	0.70±0.1	0.60±0.2	F=7.5	.003

UA: Umbilical artery.

Table (4): Baseline data of middle cerebral artery Doppler indices of the studied patients.

Variables	
Middle cerebral artery systolic/diastolic ratio (UA S/D): Mean ± SD	5.2±1.0
Middle cerebral artery pulsatility index (UA PI): Mean ± SD	1.6±0.13
Umbilical artery resistance index (UA RI): Mean ± SD	0.72±0.1

Table (5): Middle cerebral artery Doppler indices before, two hours and six hours following tadalafil therapy in the studied patients.

Variables	Pre-tadalafil n=30	Two hours-post tadalafil n=30	Six hours-post tadalafil n=30	Repeated measure ANOVA	*p*-value
MCA Systolic/ diastolic ratio: Mean ± SD	5.2±1.0	6.1±1.1	7.5±2.4	F=17.1	<.001
MCA pulsatility index: Mean ± SD	1.6±0.13	1.9±0.17	2.1±0.40	F=26.1	.<.001
MCA resistance index: Mean ± SD	0.72±0.1	0.83±0.16	0.9±0.21	F=6.5	.006

MCA: Middle cerebral artery.

Discussion

Adequate placental blood flow is essential for the optimal delivery of nutrients from mother to fetus and for growth of conceptus. Restricted fetal growth results from pathophysiological and environmental factors, which alters utero-placental blood flow, placental function and therefore, nutrient availability to the fetus **[17]**.

Vascular endothelial activation is also present in pregnancies with fetal growth restriction without preeclampsia. Pregnancies with fetal growth restriction are associated with elevated peripheral resistance in the maternal arterial system as seen in pregnancies with preeclampsia **[18]**.

A poor perinatal outcome is expected in pregnancies with high vascular resistance in uterine circulation, but the pregnancies in which the resistance values are normalized in the later trimesters have a significantly better outcome **[19]**.

In a normal pregnancy, the trophoblast produces nitric oxide (NO) which plays an important role in vasodilatation in the fetoplacental circulation to improve oxygen and nutritional supply to the fetus. Nitric oxide relaxes arterial and venous smooth muscle potently and might inhibit platelets

aggregation and adhesion. Nitric oxide donors, as vasodilating agents, must be the possible therapeutic approach for embryo development and fetus growth. The umbilical vein endothelial cells in FGR do not respond to chronic hypoxia, which may lead to fetoplacental vasoconstriction. As a locally potent vasodilator, nitric oxide helps regulate perfusion by counter balancing the effects of other vasoactive agents [20].

Moreover, increased circulating phosphodiesterase (PDE) activity is suspected in women with preeclampsia. In pregnancies with fetal growth restriction and without preeclampsia, a reversible increased myometrial arterial tone by phosphodiesterase inhibition has been reported in vitro [20].

In pregnancies with fetal growth restriction, we tried to investigate tadalafil effect on pregnancies at high risk for fetal growth restriction using Doppler indices.

This study was carried out on 30 pregnant women with a singleton pregnancy, between 29-37 weeks of gestation attending Emergency Unit of Obstetrics and Gynecology Department, Zagazig University Hospitals. This group of patients was selected according to both present and past medical disorders and past obstetric history. Umbilical artery Doppler is identified and Middle cerebral artery Doppler was found. Mean age of studied women is 30.5 years, with range from 26 to 35 year old.

Abdelshafy et al., [21] evaluated the effect of sildenafil citrate on Doppler velocity indices in patients with fetal growth restriction (FGR) associated with impaired placental circulation. A 90 women with a singleton pregnancy, between 24-34 weeks, with SGA and placental insufficiency which was diagnosed by ultrasonography measurement when the estimated fetal weight falls below the 10^{th} percentile for gestational age and abnormal umbilical artery Doppler velocimetry, were randomly assigned into either Sildenafil (n=45) or placebo group (n=45). No statistically significant differences were found between both groups regarding basal demographic, and clinical characteristics.

Ghoneim and Abo-El Roose [22] assessed whether sildenafil citrate improves blood flow in fetal umbilical arteries and middle cerebral arteries in pregnancies at high risk for fetal growth restriction. The mean age of studied population was 34.1 and 43% were mild pre-eclampsia, 17% were diabetics and 30% had history of previous FGR, stillbirth or severe pre-eclampsia and only 10% of the participants had elevated umbilical artery indices above the 90th percentile form.

In our study, there are statistically significant differences in umbilical artery Doppler indices before, two hours and six hours following tadalafil therapy in the studied patients. Also, Ghoneim and Abo-El Roose [22] showed statistically significant differences in umbilical artery Doppler indices before sildenafil and 2 and 6 hours following sildenafil citrate therapy ion the studied patients ($p<0.05$).

In our study, there are statistically significant differences in middle cerebral artery Doppler indices before, two hours and six hours following tadalafil therapy in the studied patients.

Dastjerdi et al., [8] detected no significant improvement was detected in the perfusion of umbilical and middle cerebral arteries in the control group. Mean umbilical and middle cerebral arteries pulsatility index and systolic/diastolic ratio were similar before and after placebo. They concluded that velocimetry index values reflect decreased placental bed vascular resistance after Sildenafil. Sildenafil citrate can improve fetoplacental perfusion in pregnancies complicated by intrauterine growth restriction. It could be a potential therapeutic strategy to improve uteroplacental blood flow in pregnancies with fetal growth restriction (FGR).

Von Dadelszen et al., [6] studied the role of sildenafil citrate therapy for severe early onset intrauterine growth restriction. Women were offered sildenafil citrate 25mg three times daily until delivery if their pregnancy was complicated by early onset IUGR and either the gestational age was less than 25 weeks or the fetal weight was 600g. They found that sildenafil growth was associated with increased AC growth. They suggested that Sildenafil treatment may offer a new opportunity to improve perinatal outcomes for women whose pregnancies are complicated by severe early-onset IUGR.

Panda et al., [23] stated that sildenafil, as a vasodilator has also emerged as a potential management option in the treatment of FGR and preeclampsia by later normalization in velocimetric profile.

Umekawa et al., [24] evaluated the efficacy and safety of tadalafil against FGR and demonstrated that both fetal growth velocity from enrolment to birth and birth weight were significantly higher in the tadalafil group than in the conventional management group.

Walton et al., **[25]** compared the efficacy of these 2 PDE5 inhibitors for reversing vasoconstriction in an ex vivo human placental model and evaluating molecular and physiological responses. They indicated a decrease arterial pressure with sildenafil citrate compared with controls, whereas tadalafil showed no difference. PDE5 and endothelial nitric oxide synthase activity were altered with sildenafil but not tadalafil. Sildenafil citrate improved preconstricted placental arterial perfusion in a human placental model, whereas tadalafil showed no response. It is possible that tadalafil did not cross the human placental barrier or was degraded by trophoblasts.

Improvement in doppler indices, pregnancy prolongation, increased gestational age at delivery, improved neonatal weight were also described by El Sayed et al., **[7]**.

Abdelshafy et al., **[21]** concluded that the use of sildenafil citrate in pregnancies with fetal growth restriction (FGR) improved the feto-placental Doppler indices and improved neonatal outcomes.

Tanaka et al., **[26]** identified the relationship between the serum concentration of tadalafil and uterine artery blood flow in pregnant women. They concluded that the blood concentration and uterine artery blood flow fluctuate in parallel, the latter was decreased by reduced blood concentration. Thus, a study of tadalafil administered twice a day in pregnantwomen will be needed to stabilize uterine artery blood flow.

This study was limited by not assessing the long term effect of tadalafil on the neonatal morbidity and mortality, it is hopeful that future trials would be designed assess those outcomes. Also, we did not measure the serum maternal tadalafil concentrations during therapy to reach the most appropriate dose of tadalafil therapy with the effective concentrations known to dilate maternal uteroplacental vascular endothelium.

Conclusion:

In the light of the above results, we concluded that administration of tadalafil hourly in pregnancies with fetal growth restriction (FGR) improved the fetoplacental Doppler indices (pulsatility index of umbilical artery and middle cerebral artery) and improved neonatal outcomes. Therefore, tadalafil treatment may offer a promising therapy for fetal growth restriction with placental insufficiency.

Conflicts of interest:

There are no conflicts of interest.

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تأثير عقار التادلافيل على مقاومة التدفق الدموى فى الشريان السرى والشريان الدماغى الأوسط لحالات الحمل المعرضة لخطر تقييد نمو الجنين

المقدمة: يعد تقييد نمو الجنين من المضاعفات الخطيرة والتى قد توثر سلبياً على الجنين أثناء الحمل والولادة وما بعدها. وقد وجد أن موسعات الأوعية الدموية من مجموعة مثبطات الفوسفودای إستراز (مثل السيلدينافيل والتادلافيل) لها دور هام فى الوقاية من هذه المشكلة.

الهدف من البحث: إستخدام عقار التادلافيل فى الوقاية من تقييد نمو الجنين للحالات المعرضة لذلك.

خطوات البحث: تمت هذه الدراسة على ٣٠ حامل من المعرضات لخطر تأخر نمو الجنين بوحدة الحمل الحرج بمستشفيات جامعة الزقازيق.

النتائج: تغيرات إيجابية فى التدفق الدموى المشيمى والدماغى بعد ساعات من استخدام التادلافيل والذى يجعله دواء هام فى الوقاية من تقييد أو تأخر نمو الجنين.