

Evaluation of Progesterone Effects on Fetal Doppler Velocimetry

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Abstract

Background: Progesterone is a smooth muscle relaxant and also has a vasodilator effect on human placental arteries and veins.

Objectives: The aim of this study was to evaluate the effect of progesterone therapy on fetal Doppler velocimetry in intrauterine growth retardation (IUGR) and preterm fetuses.

Methods: Thirty pregnant females with IUGR and thirty pregnant females with threatened preterm labor at 28 to 37 weeks of gestation were enrolled in the clinical trial study. Fetal Doppler velocimetry was investigated before, 24 hours and two weeks after progesterone therapy. Seven patients with IUGR and 9 patients with preterm labor were excluded from the study before completion of the survey due to the termination of pregnancy.

Results: Following progesterone treatment, middle cerebral artery pulsatility index (MCA-PI) significantly decreased after 24 hours in patients with IUGR and after two weeks in patients with preterm labor ($P < 0.001$). There was not a statistically significant decrease in the pulsatility index of the fetal umbilical artery (UaA) after 24 hours in the IUGR fetuses ($P = 0.18$). Umbilical artery pulsatility index (UaA-PI) significantly decreased after two weeks in IUGR fetuses ($P < 0.004$).

Conclusions: Progesterone led to a reduction in the MCA-PI and UaA-PI in IUGR and preterm fetuses. Vasodilatory effect of progesterone on the umbilical artery is mediated by multiple doses in IUGR fetuses.

Keywords: Doppler Flow Velocimetry, Intrauterine Growth Retardation, Pulsatility Index, Progesterone

1. Background

Intrauterine growth retardation (IUGR) is a great health concern worldwide. It affects 5 to 10% of pregnancies and is a major cause of prenatal mortality and morbidity (1, 2). There is no known cure for this gestational disease and tackling the condition remains a serious problem for perinatology science (3). There are various premature and prolonged complications of IUGR. In addition to increased risk of Intrauterine fetal death (IUFD) at each gestational age, after-birth complications like metabolic disorders, hematologic complications, and respiratory distress syndrome, necrotizing enterocolitis and premature retinopathy are observed (4-7). Despite the unknown basis of this disorder, the most prevalent risk factor of developing the disease (particularly prolonged type) is an utero-placental dysfunction that leads to a reduction in placental blood flow, and an increase of vessel resistance in the fetus. This resistance increase is the hallmark of the disorder and is indicated by elevated constriction in placental resistant arteries (8). The likely causes of this elevated vasoconstriction include defective trophoblast invasion and reduced endothelial nitric oxide (NO) (3, 8, 9).

Progesterone is a smooth muscle relaxant and has a

vasodilator effect on vasculature. Progesterone causes a dose-dependent endothelium-independent relaxation of human placental arteries and veins. This relaxation seems to be mediated by a receptor-activated cyclic adenosine monophosphate (CAMP) mechanism and could be physiologically important in maintaining low resistance and adequate blood flow in the placental circulation (10).

2. Objectives

The aim of this study was to evaluate the effect of the vasodilatory effects of progesterone on fetal Doppler velocimetry in IUGR and preterm fetuses.

3. Methods

This study had a prospective clinical trial design and was conducted in the perinatology department of Valiasr teaching hospital from November 2012 to January 2013.

Thirty singleton pregnant females with IUGR and thirty singleton pregnant females with threaten preterm labor were enrolled in the study. The study protocol was approved by the ethics committee of Tehran University of Medical Sciences.

Informed consent was obtained from participants before enrollment in the study. Inclusion criteria were singleton pregnancy, 28 to 37 weeks of gestation, and a known gestational age.

Inclusion criteria of IUGR were singleton pregnancy, birth weight of below the 10th percentile for gestational age, abdominal circumference < 10th percentile and normal fetal Doppler velocimetry. Criteria to enter in the threatened preterm labor group were regular uterine contractions or cervical changes or short cervix without premature rupture of membranes (PROM). Following admission, if it was necessary to enhance respiratory maturity, the patients received tocolytic agents like nifedipine and steroids betamethasone, according to American College of Obstetricians and Gynecologists (ACOG) protocol (10). Only mothers entered the study that had stopped taking the above-mentioned drugs for 24 to 48 hours (to remove the drug's effects on vascular flow) and had no contraindication for receiving progesterone. Females with pregnancies involving fetal anomalies or chromosomal abnormalities, intake of progesterone and vasodilator agents for other treatment, were excluded.

Vaginal progesterone (400 mg daily for two weeks) was administered to patients (10).

All patients underwent biometric ultrasonography and Doppler velocimetry measurements. Doppler velocimetry was carried out with a commercially available instrument (SIMENSE multi-frequency, ACUSON X700 ultrasound system, Germany) using a 3.5-5 MHz convex probe.

Doppler flow assessment of the fetal circulation was conducted by an independent investigator blinded to the treatment, before and 24 hours and two weeks after the administration of progesterone.

Sonography was carried out for all patients during all three stages by the same operator. The studied variables were pulsatility index (PI) for the umbilical artery and the middle cerebral artery.

Decisions about pregnancy termination (therapeutic delivery) were made using the ACOG clinical guideline.

3.1. Statistical Analysis

Variable were shown using mean \pm standard deviation. The SPSS statistical software, version 16 (IBM, Armonk, NY, USA) was used for statistical analysis. The Mann-Whitney U-test was used to compare two independent non-parametric continuous variables, and the Wilcoxon sign-rank test was used to compare two paired non-parametric continuous variables. A P-value of less than 0.05 was considered statistically significant.

4. Results

Sixty pregnant females were included in the study. All patients with IUGR or preterm labor had the same maternal age, gravity and gestational age. During the study, 16 patients were excluded from the study before completion of the survey due to the termination of pregnancy.

Seven patients with IUGR (23.3%) terminated due to fetal distress. Nine patients with preterm labor (30%) had deliveries before completion of the two weeks progesterone therapy. Furthermore, 23 patients with IUGR and 21 patients with preterm labor were followed after two weeks of progesterone therapy. Following progesterone treatment, there was a statistically significant decrease in the pulsatility index of the fetal umbilical artery in both patients with IUGR and preterm labor after two weeks.

In the 23 patients with IUGR, fetal umbilical artery PI was not significantly different before and 24 hours after progesterone therapy ($P = 0.18$).

Fetal umbilical artery PI was significantly different before and after the 24-hour treatment in the 21 patients with preterm labor ($P = 0.004$).

Pulsatility index of the middle cerebral artery decreased after 24-hour and two-week progesterone therapy for both patients with IUGR and preterm labor ($P = 0.001$) (Table 1).

Following progesterone treatment, mean change of pulsatility index of the fetal umbilical artery in patients with IUGR and preterm labor after 2 weeks were 0.14 and 0.17.

Mean change of MCA pulsatility index in patients with IUGR and preterm labor after two weeks of treatment were 0.58 and 0.51 (Figures 1 and 2).

5. Discussion

In this study, the effect of progesterone on vascular doppler in IUGR and preterm fetus was investigated. The results showed a reduction of umbilical artery PI two weeks after the administration of vaginal progesterone in both patients with preterm labor and IUGR. Mean change of umbilical artery PI in IUGR fetuses was less than patients with preterm labor after 2 weeks of treatment ($P = 0.14$ vs $P = 0.17$).

A remarkable reduction was observed in fetal middle umbilical artery PI after 24 hours and two weeks of treatment in all patients. An average variation of middle umbilical artery PI in the IUGR fetuses after two weeks was higher than in the preterm group ($P = 0.58$ vs $P = 0.51$).

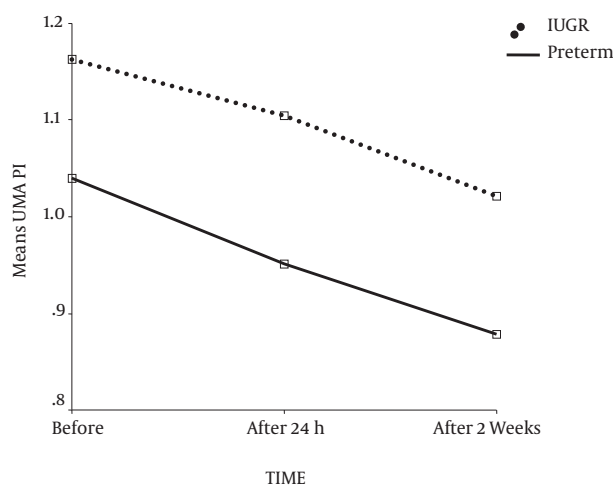
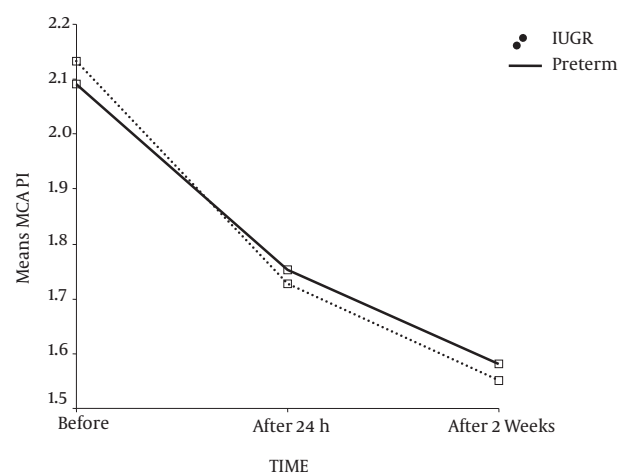
This reduction of the fetal umbilical artery PI and the middle umbilical artery PI implies a reduction in resistance of current flow in fetal umbilical artery. Vasodila-

Table 1. Doppler Flow Parameters of Fetal Circulation Before and After Progesterone Treatment in Pregnancies With Intrauterine Growth Retardation and Threatened Preterm Labor

Variable IUGR (n:23)	Before Progesterone Treatment (Mean \pm SD)	After 24 Hours Progesterone Treatment (Mean \pm SD)	P-Value	After 2 Weeks Progesterone Treatment (Mean \pm SD)	P-Value ^a
UMA-PI	1.16 \pm 0.24	1.10 \pm 0.29	0/18	1.02 \pm 0.29	< 0.004
UMA-RI	0.67 \pm 0.08	0.61 \pm 0.08	< 0.001	0.55 \pm 0.09	< 0.001
MCA-PI	2.13 \pm 0.44	1.72 \pm 0.43	< 0.001	1.55 \pm 0.43	< 0.001
MCA-RI	0.84 \pm 0.07	0.74 \pm 0.08	< 0.001	0.67 \pm 0.08	< 0.001
Preterm birth (n:21)					
UMA-PI	1.04 \pm 0.16	0.95 \pm 0.17	< 0.001	0.87 \pm 0.17	< 0.004
UMA-RI	0.61 \pm 0.06	0.58 \pm 0.08	< 0.001	0.48 \pm 0.09	< 0.001
MCA-PI	2.09 \pm 0.31	1.75 \pm 0.32	< 0.001	1.58 \pm 0.32	< 0.001
MCA-RI	0.85 \pm 0.05	0.74 \pm 0.06	< 0.001	0.65 \pm 0.08	< 0.001

Abbreviations: MCA, middle cerebral artery; PI, pulsatility index; RI, resistance index; S/D, systolic-to-diastolic ratio; UA, umbilical artery.

^aP \leq 0.05 statistically significant.

**Figure 1.** Mean Umbilical Artery Pulsatility Index Before, After 24 Hours and Two Weeks of Progesterone Therapy**Figure 2.** Mean Middle Cerebral Artery Pulsatility Index Before, After 24 Hours and Two Weeks of Progesterone Therapy

tory effect of progesterone reduces vessel resistance. The reduction of fetal middle umbilical artery PI was more apparent compared to the umbilical artery PI, probably due to higher sensitivity of the fetal middle cerebral artery to progesterone within the development period.

Vasodilatory effect of progesterone was shown in previous study (11, 12). Omar et al., investigated the effect of progesterone on vascular placental tone and confirmed the arteriovenous vasodilation effect of increased doses of progesterone (13).

Hermenegildo et al. study demonstrated that progesterone and medroxyprogesterone acetate induced prosta-

cyclin synthesis through dose and receptor related pathways in human umbilical venous endothelial cells. Progesterone increased endothelial prostacyclin by enhancing cyclooxygenase-1 and 2 expressions and activity (12)

Barda et al. investigated the effect of single-dose progesterone on Doppler velocimetry of umbilical and middle cerebral arteries and uterine artery during pregnancy with preterm labor. The study of Barda et al. showed a reduction in middle cerebral artery PI and RI and a reduction in uterine artery RI, which implied the vasodilatory effect of progesterone (10).

Our results showed that middle cerebral artery PI decreased in patients with preterm labor after 24 hours,

which is similar to the study of Barda et al. However, in our study umbilical artery PI did not decrease after 24 hours (single dose) in IUGR fetuses ($P = 0.18$). The reduction of the umbilical artery PI was seen after two weeks ($P = 0.001$). Our results demonstrated that vasodilatory effect of progesterone on the umbilical artery was mediated by multiple doses in IUGR fetuses.

The positive vasodilatory effect of progesterone on the umbilical artery and the middle cerebral artery of the fetus seems to be a promising finding for enhancing blood supply to the fetus. Currently, there are no standard prenatal therapies, which are designed to specifically improve fetal growth or reverse the complications of IUGR. Therefore, it is evident that any successful prenatal therapies have the potential to improve mortality and reduce short and long term complications of both IUGR and prematurity.

The present study indicated the vasodilatory effect of vaginal progesterone on umbilical and cerebral vessels of a fetus with IUGR. Therefore, prenatal therapies with progesterone may reverse abnormal fetal Doppler velocimetry and improve fetal growth. This effect reduces the complications of IUGR.

Safety and possible additional benefits of this intervention need to be investigated by further studies. Further studies with higher sample sizes are required to access advantages and disadvantages of prolonged use of progesterone for IUGR fetuses to offer therapeutic procedures for reduction in complications of these high-risk pregnancies.

5.1. Conclusion

The use of progesterone led to a reduction in the middle cerebral artery and the umbilical artery PI. Vaginal progesterone can improve fetoplacental perfusion in pregnancies complicated by IUGR and preterm labor.

Footnote

Conflict of Interest: There was no conflict of interest.

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