Antenatal dexamethasone effect on Doppler blood flow velocity in women at risk for preterm birth: prospective case series

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Abstract
Background: Maternal administration of corticosteroids is essential to improve fetal lung surfactant production and hasten the fetal lung maturity in women at risk for preterm birth.

Objectives: The current study aims to evaluate the effects of dexamethasone on fetal and uteroplacental circulation in pregnancies at risk for preterm birth after 24 hours of its administration.

Methods: A prospective cross-sectional study was carried out in a tertiary University Hospital and included 52 pregnant women with singleton pregnancies. Doppler studies were performed on maternal uterine arteries, umbilical artery, fetal middle cerebral artery (MCA) and fetal descending aorta and just before dexamethasone administration and repeated 24 hours after completion of the course.

Results: There was a statistically significant difference between all Doppler indices in the umbilical artery (PI= 1.09±0.4 and 1.05±0.39, RI= 0.66±0.14 and 0.63±0.14; p=0.001), fetal MCA (RI= 0.86±0.12 and 0.83±0.13, PI= 2.19±0.72 and 2.15±0.72; p=0.001) and aorta (RI= 0.9±0.55 and 0.87±0.55; p=0.001, PI= 1.91±0.44 and 1.89±0.44; p=0.040) in comparison before and 24 hours after maternal dexamethasone administration respectively. Also uterine artery PI was significantly different (0.9±0.27 and 0.87±0.26; p=0.001).

Conclusion: Antenatal dexamethasone for women at risk of preterm birth improves the fetal and uteroplacental blood flow at 24 hours after its administration.

Keywords: Doppler; preterm birth; corticosteroids; dexamethasone.

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Introduction
Respiratory distress syndrome (RDS) is one of the major causes of early neonatal morbidity and mortality especially in developing countries1. Antenatal administration of corticosteroids for women at risk for preterm birth is the main line to improve fetal lung surfactant production and enhance the fetal lung maturity2. Besides that, they reduce the incidence of intraventricular hemorrhage, necrotizing enterocolitis and overall neonatal mortality in preterm infants3. Dexamethasone is generally safe during pregnancy. Unlike betamethasone, some studies reported reduction in fetal body movements, fetal breathing movements and heart rate variation after administration4,5. Repeated courses of steroids have been associated with increased risk of fetal growth restriction6. Therefore, assessment of fetal hemodynamic status after corticosteroid administration by Doppler is essential.

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Previous studies showed conflicting results regarding this important subject and most of them were focusing on the effect of steroids on pregnancies complicated with intrauterine growth restriction (IUGR)\textsuperscript{7-9}. Also, most of previous studies investigated the effect of betamethasone on fetal and uteroplacental blood flow\textsuperscript{4,5,10,11}, few studies only investigated the effect of dexamethasone\textsuperscript{12}. Therefore, the present study aims to investigate the effects of dexamethasone on fetal and uteroplacental circulation in pregnant women at risk for preterm birth after 24 hours of its administration.

Methods
Study setting and design
The current study was a prospective cross-sectional study carried out in a tertiary University Hospital in Egypt between January to December 2014. The study was approved by the institutional Ethical Review Board and written consent obtained from all study participants.

Study participants
Eligible participants were pregnant women with gestational age from 24 to 34 weeks and at risk for preterm birth. Gestational age was calculated according to the date of the last menstrual period and confirmed by first trimester ultrasound. Patients at risk of preterm labor included were those with preterm uterine contractions, placenta previa, and pre-eclampsia. Meanwhile, Patients who were actively in labor, presented with premature rupture of membranes, intrauterine growth restriction (IUGR), those who had received corticosteroids in their pregnancies and/or fetuses with suspected structural abnormalities were excluded from participation. Women who had any contraindication of corticosteroids administration had also been excluded.

Study intervention
Eligible participants were evaluated through full history taking and detailed anatomical scan by level II sonographer before inclusion to confirm their gestational age and exclude any structural anomalies.

Each woman received the recommended course of corticosteroids to induce fetal lung maturity consisting of two doses of 12 mg dexamethasone (Dexamethazone 8 ml, Sigma Pharam, Egypt) intramuscularly 12 hours apart. Doppler studies were performed just before dexamethasone administration and repeated 24 hours after completion of the dexamethasone course using a SonoAce X6 machine (Medison, Korea) with 3.75 MHz transabdominal probe. All patients underwent Doppler examination by 2 different level II sonographers.

Doppler examination was done with the fetus in a quiet state, in absent of fetal movements and fetal breathing movements. The angle of insonation was optimized to be as low as possible, never exceeding 45\degree. The sweep speed was 2.5 cm/s and the pulse repetition frequency ranged from 3.5 - 5.5 Khz. The Doppler spectrum was recorded during maternal voluntary apnea.

Blood flow velocity waveforms were obtained from the umbilical artery, fetal middle cerebral artery (MCA), fetal descending aorta and maternal uterine arteries. Spectral pulsed wave Doppler analysis was done after that; RI and PI were calculated for each vessel. The formulas used for PI and RI were $PI = (S-D)/mean$ and $RI = (S-D)/S$ respectively, when S is the peak Doppler frequency shift and D is the minimum. At least 5 uniform waves forms of the spectrum were recorded and analyzed.

Blood flow velocity waveforms were recorded from the umbilical artery in the free floating mid-portion of the umbilical cord\textsuperscript{13}. Doppler signals registered from the fetal MCA in its proximal third. The MCA vessels were located with color Doppler ultrasound overlying the anterior wing of the sphenoid bone near the base of the skull\textsuperscript{14}. Doppler signals obtained from the uterine arteries in the region of the lower uterine segment. Insonation of the uterine artery was done at its crossover the iliac artery\textsuperscript{15}. Velocity waveforms from the fetal descending aorta were recorded at the lower thoracic level just above the diaphragm, keeping the angle of insonation of the Doppler beam below 45\degree.

The primary outcome of the study was detection of changes in Doppler indices before and after dexamethasone administration.

Statistical analysis
Analysis of data was done using SPSS Inc., (Statistical Program for Social Science Inc.,) Chicago, IL, USA, version 22. Qualitative variables were expressed as frequency and percentage. Quantitative variables were expressed in terms of, mean, standard deviation and range. For quantitative data, comparison between the Doppler results in
the same group was done using paired t-test. Level of significance "P" value was evaluated, where P value < 0.05 was considered statistically significant.

**Results**
The study included 52 participants at risk of preterm birth. We anticipated the risk of preterm birth on the basis of preterm uterine contractions (n=33), placenta previa (n=13) and pre-eclampsia (n=6)
The demographic data are presented in Table 1. The mean age of the study group was 27.7±4.5 years. At the time of dexamethasone administration, mean gestational age was 30.9±2.7 weeks, and in 17 (32.7%) pregnancies, gestational age was <30 weeks.

**Table 1. Maternal and neonatal characteristics of the study participants.**

| Maternal characteristics                      |                  |
|-----------------------------------------------|------------------|
| **Age (years); mean ±SD**                     | 27.7 ± 4.5       |
| **Parity; median (Range)**                    | 4 (0 – 7)        |
| **Gestational age (weeks+days)**              |                  |
| At examination; mean ± SD (Range)             | 30.7 ± 2.5 (24+1 to 33+5) |
| At delivery; mean ± SD (Range)                | 31.1 ± 2.6 (24+4 to 36+3) |

| Neonatal characteristics                      |                  |
|-----------------------------------------------|------------------|
| **Birth weight (gm); mean ± SD**              | 1135.3 ± 750.22  |
| **Referral to PCU; n (%)**                    | 30 (57.7)        |
| **1 minute Apgar score < 7; n (%)**           | 35 (67.3)        |
| **5 minutes Apgar score < 7; n (%)**          | 21 (40.4)        |
| **Female gender; n (%)**                      | 34 (65.4)        |

PCU: pediatric care unit

Twenty-three (44.2%) of the study participants delivered within 4 days after receiving the full dose of dexamethasone. Eleven (21.2%) women delivered after 5–7 days, nine (17.3%) women delivered between 8-15 days and finally seven (13.5%) women continued pregnancy more than 2 weeks after end of the course. Cesarean sections were performed in 35 (67.3%) patients. Only one stillbirth was delivered vaginally due to placental abruption in association with pre-eclampsia.

Table 2 shows the results of Doppler indices in different sub-groups of the study participants.

Overall, there was a statistically significant difference between all Doppler indices in umbilical artery (PI=1.09±0.4 and 1.05±0.39, RI= 0.66±0.14 and 0.63±0.14; p=0.001), fetal MCA (RI= 0.86±0.12 and 0.83±0.13, PI= 2.19±0.72 and 2.15±0.72; p=0.001) and aorta (RI= 0.9±0.55 and 0.87±0.55; p=0.001, PI= 1.91±0.44 and 1.89±0.44; p=0.040) in comparison before and 24 hours after maternal dexamethasone administration respectively. Also uterine artery PI was significantly different (0.9±0.27 and 0.87±0.26; p=0.001), while no significant difference in uterine artery RI
Table 2. Fetal and uteroplacental Doppler indices before and 24 hours after dexamethasone administration in the different groups.

| Doppler indices | Threatened preterm labor (n=33) | Preeclampsia (n=13) | Placenta previa (n=6) | p-value |
|-----------------|---------------------------------|---------------------|----------------------|---------|
|                 | Before Dexamethasone | 24 hours after Dexamethasone | Before Dexamethasone | 24 hours after Dexamethasone | Before Dexamethasone | 24 hours after Dexamethasone |
| Umbilical artery PI | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD |
|                   | 1.04 ± 0.4 | 1.01 ± 0.21 | 1.11 ± 0.36 | 1.06 ± 0.42 | 1.09 ± 0.26 | 1.03 ± 0.33 |
| Umbilical artery RI | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD |
|                   | 0.67 ± 0.19 | 0.63 ± 0.17 | 0.69 ± 0.21 | 0.65 ± 0.17 | 0.64 ± 0.13 | 0.62 ± 0.14 |
| Fetal aorta PI | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD |
|                   | 1.92 ± 0.6 | 1.89 ± 0.31 | 1.91 ± 0.35 | 1.87 ± 0.43 | 1.90 ± 0.46 | 1.88 ± 0.32 |
| Fetal aorta RI | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD |
|                   | 0.9 ± 0.51 | 0.88 ± 0.46 | 0.92 ± 0.5 | 0.86 ± 0.11 | 0.91 ± 0.55 | 0.88 ± 0.44 |
| Fetal MCA PI | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD |
|                   | 2.18 ± 0.56 | 2.15 ± 0.12 | 2.19 ± 0.3 | 2.16 ± 0.55 | 2.19 ± 0.1 | 2.15 ± 0.31 |
| Fetal MCA RI | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD |
|                   | 0.87 ± 0.33 | 0.84 ± 0.57 | 0.86 ± 0.25 | 0.83 ± 0.3 | 0.85 ± 0.70 | 0.83 ± 0.66 |
| Uterine artery PI | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD |
|                   | 0.91 ± 0.29 | 0.88 ± 0.54 | 0.9 ± 0.13 | 0.87 ± 0.2 | 0.89 ± 0.27 | 0.87 ± 0.21 |
| Uterine artery RI | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD |
|                   | 0.58 ± 0.21 | 0.57 ± 0.11 | 0.56 ± 0.11 | 0.54 ± 0.78 | 0.57 ± 0.34 | 0.54 ± 0.23 |

MCA; middle cerebral artery, PA; pulsatility index, RI; resistance index.

Discussion

In this study, dexamethasone administration was found to have a beneficial effect on fetuses at risk for preterm birth as evident by the decrease in the Doppler indices of umbilical artery, fetal descending aorta, MCA and uterine artery. Umbilical artery Doppler indices showed statistically significant reduction 24 hours after dexamethasone administration. Our results agreed with Wallace and Baker’s study that reported an association between betamethasone treatment and decreased placental vascular resistance as reflected by waveforms obtained from umbilical artery16. This is similarly agreed by Nozaki et al who found a reduction in the umbilical artery PI within 24 hours following antenatal corticosteroid therapy9.

With regard to fetal descending Aorta Doppler indices of our study population demonstrated significant reduction in the vascular resistance after dexamethasone administration. To the best of our knowledge, the current study was the first to describe a decrease in PI and RI of the descending Aorta 24 hours after antenatal dexamethasone administration.

MCA Doppler indices decreased after the treatment. These findings are in agreement with the results of Chitrit et al who observed a transient and significant decrease in fetal MCA (PI, RI) after maternal dexamethasone administration12. However some studies disagree with our results as Senat and Ville and Wijnberger et al, but they were on growth-restricted preterm fetuses; no effect was found from betamethasone on PI in fetal MCA7,8. In the latter study, circulation in fetuses was studied for up to 14 days, indicating that placental insufficiency was probably not severe enough to indicate early delivery. Moreover, Senat and Ville examined the effect of steroids on blood flow waveforms in IUGR fetuses and found no significant changes of PI, RI values in the different vessels after dexamethasone course.

There was statistical significant reduction in the uterine artery Doppler indices before and 24 hours after dexamethasone administration in the present study. These findings are in agreement with data published by Chitrit et al who observed similar transient and significant decrease in uterine artery PI and RI after maternal dexamethasone administration in healthy fetus11. However, Thuring et al reported that there was no significant influence of betamethasone therapy on Doppler indices in uterine circulation in pregnancies with imminent preterm delivery16.
A study on human placentas by Clifton et al showed that the mechanism behind dexamethasone-induced vasodilation might be an endothelium independent mechanism, as they did not find any involvement of endothelium-derived products such as prostaglandin I2 and nitric oxide17. One of the limitations of the current study is that umbilical artery PH was not measured after delivery for accurate assessment of neonatal outcome due to low facilities in our hospital, so we depended only on Apgar score.

In conclusion, administration of dexamethasone to pregnant women at risk of preterm birth could improve the blood flow in the uterine arteries, fetal MCA, descending aorta and umbilical artery 24 hours after its administration. The valuable effect of its administration is constant regardless of the gestational age and fetal weight.

Conflict of interest

The authors declare that they have no conflict of interest.

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