



Comparison Between Changes In Doppler Indices In Intrauterine Growth Retardation Before And After Dexamethasone Administration

Mohammed Nagy Mohesen ^a, Hamada Ashry Abdel-wahed ^b, Ahmed Adel Yasseen ^c

Obstetrics and Gynecology department, Faculty of Medicine, Beni-Suef University, Egypt

Abstract:

Background: Intrauterine growth restriction (IUGR) is associated with stillbirth, neonatal death, and perinatal morbidity. In the majority of cases, IUGR is due to placental insufficiency but may also be due to a number of other conditions for example congenital anomalies, infections, or drug and substance misuse. There is no method for precise identification of intrauterine growth restricted babies antenatally. The most critical decision is the timing of delivery of those restricted fetuses. There is no current treatment available for intrauterine growth restriction (IUGR); the only management option obstetricians can offer is early birth. **Objectives:** The aim of this work is to detect any change in the cerebroplacental Doppler ratio in IUGR fetuses before and after receiving Dexamethasone. **Setting:** Department of Obstetrics &Gynecology, Beni-Suef University Hospital. **Methods:** The present study was designed as a Prospective Study including 100 pregnant women diagnosed as IUGR. The cases were offered Dexamethasone 8 mg / intramuscular every 12 hours for 48 hours. We excluded patients with multiple pregnancies, fetal congenital anomalies, and maternal diabetes mellitus as co-morbidity and maternal use of heparin, low dose aspirin or if there is planned termination of pregnancy. All patients underwent ultrasonography to determine gestational age and presence of IUGR and we measured the Doppler indices and biophysical profile. Then Doppler indices repeated again after 12 hours and 24 hours of receiving last dose of dexamethasone.. **Results:**The results show significant statistical difference in UA, MCA and also cerebroplacental ratio significantly decreased at the end of study in indices before and after dexamethasone administration. **Conclusions:** The current study finds in healthy fetuses a transient, significant and unexplained decrease in fetal middle cerebral artery impedance on the fourth day following maternal dexamethasone administration.

Keywords: IUGR, dexamethasone, Doppler indices.

1. Introduction:

According to American Congress of Obstetricians & Gynecologists (ACOG), intrauterine growth retardation (IUGR) is one of the most common and complex problems in modern obstetrics, while there are several definitions of IUGR, the most widely accepted is a fetus whose estimated weight is below the 10th percentile for its gestational age and whose abdominal circumference is below the 2.5th percentile (2).

IUGR may result in significant fetal morbidity and mortality if not properly diagnosed. The condition is most commonly caused by inadequate maternal-fetal circulation, with a resultant decrease in fetal growth (2).

Approximately 20 % of IUGR infants are symmetrically small with a relatively proportionate decrease in many organ weights. 80% are asymmetrically small, with relative sparing of brain weight, especially when compared with that of the liver or thymus (14). There are different methods of screening for IUGR as: The symphysis –fundal height measurement (SFH), customized growth curve, ultrasound examination and biochemical screening.

Ultrasound examination: Suspected growth restriction could be further evaluated by detailed ultrasound of fetus to identify fetal anomalies in addition to biometry.

Biochemical screening: In first trimester, unexplained low pregnancy – associated plasma

protein A (PAPP-A) or human chorionic gonadotropin (HCG), and the unexplained elevation in serum AFP, HCG, or inhibin A, or low estriol in second trimester, could be associated with birth weight <10th percentile.

Maternal antenatal administration for synthetic corticosteroids (betamethasone or dexamethasone) has been used for long time to improve fetal lung surfactant production and hasten the fetal lung maturity in women at risk for preterm birth (3).

Corticosteroids also reduce the occurrence of RDS, intraventricular hemorrhage, necrotizing enterocolitis and overall neonatal mortality in preterm infants. No serious side effects have been reported reduction in fetal body movements, fetal breathing movements and heart rate variation after corticosteroids administration (3).

Pregnancies affected by fetal growth restriction between 24+0 and 35+6 weeks of gestation at risk of delivery should receive a single course of antenatal corticosteroids (11).

Antenatal corticosteroids administration improves end diastolic blood flow of umbilical artery in fetuses with IUGR or placental insufficiency symptoms (5).

Antepartum surveillance with Doppler of the umbilical artery should be started when the fetus is viable and IUGR is suspected. Doppler

studies of vessels other than the umbilical artery, as part of assessment of fetal well-being in pregnancies complicated by IUGR, should be reserved for research protocols (2).

The middle cerebral artery is the vessel of choice to assess the fetal cerebral circulation because it is easy to identify, has a high reproducibility, and provides information on the brain-sparing effect. The circulation, represent major branches of the circle of Willis and are the most accessible cerebral vessels for ultrasound imaging in the fetuses (1).

In pregnancies complicated by absent end diastolic flow in the umbilical artery, maternally administered corticosteroids induces a return in umbilical artery end-diastolic flow as early as 4 hours, along with widespread vasodilatation throughout the fetoplacental vasculature (5).

These effects are more obvious with betamethasone than dexamethasone. Repeated courses of steroids have been associated with increased risk of fetal growth restriction (7).

2. Patients and Methods:

This was a randomized study performed in Beni-Suef university hospital from January 2019 till January 2020 involving 100 women, consents were obtained.

2.1 Inclusion criteria:

1. Certain LMP (Last menstrual period).
2. Regular menstrual pattern before pregnancy.

3. Singleton pregnancy, between 28: 34 weeks gestation.

4. Spontaneous pregnancy or pregnancy after assisted reproductive technique.

5. Cases with hypertension with pregnancy were included.

2.2 Exclusion criteria:

1. Uncertain gestational age.
2. Fetuses with congenital anomaly.
3. Multiple pregnancies.
4. Maternal use of heparin.
5. Maternal diabetes mellitus.

2.3 All patients were subjected to: All women were subjected to:

A. At the first antenatal visit;

1. Thorough history taking and examination.
2. Investigations: Complete blood picture (CBC), bleeding profile, kidney function tests and liver function tests was done.
3. Ultrasound: 2D Ultrasound (Mindray N2) assessing :

It was carried out in Gynecology and Obstetrics department in Beni-Suef University Hospital, ultrasonography criteria: Ultrasound biometry of the fetus is now the gold standard for assessing fetal growth. The measurements most commonly used are the biparietal diameter, head circumference, abdominal circumference and femur length. Percentiles have been established for each of these parameters, and fetal weight can be calculated. The most sensitive indicator of symmetric and asymmetric IUGR is the abdominal

circumference, which has a sensitivity of over 95 percent if the measurement is below the 2.5th percentile. Accurate dating of the pregnancy is essential in the use of any parameter. In the absence of reliable dating, serial scans at two-or three weeks intervals must be performed to identify IUGR. It should always be remembered that each parameter measured has an error potential of about one week up to 20 gestational weeks, about two weeks from 20 to 36 weeks of gestation, and about three weeks thereafter (10).

IUGR was diagnosed by one or more of the following criteria:

1. Lag of two weeks or more between the current biometric measures (BPD, AC, FL) and documented crown rump length or certain last menstrual period.
2. <5mm increase in abdominal circumference after two weeks follow up.
3. < 200 g increase in fetal weight after two weeks follow up.
4. Trans cerebellar diameter / abdominal circumference ratio (TCD/AC) > 15%.

Selected cases were subjected to perform fetal doppler to measure umbilical artery doppler indices and middle cerebral artery doppler indices, and then patient received corticosteroids, the corticosteroids to be used is dexamethasone 8 mg every 12 hours for 48 hours (11).

Then Doppler indices repeated again after 12 hours and 24 hours of receiving last dose of dexamethasone.

Statistical methodology:

Data was statistically described in terms of mean \pm standard deviation (\pm SD), frequencies (number of cases) and relative frequencies (percentages) when appropriate.

The normal distribution of continuous variables of the demographic data was evaluated with the use of the Kolmogorov-Smirnov test. Comparison of numerical variables between the study groups will be analyzed with the independent-samples t test (when the data showed normal distribution) and using Mann-Whitney U test for data which are not normally distributed.

For comparing categorical data as all complications e.g. expulsion rates, bleeding, pregnancy etc. Chi square (χ^2) test was performed, and for small sample sizes, Fisher's Exact Test will be used as appropriate.

Statistical significance was set at a probability value (P value ≤ 0.05).

The Statistics Package for Social Science (version 22; SPSS Inc) was used for all statistical analyses.

3. Results:

A prospective randomized control study conducted at obstetrics and gynecology department of Beni-Suef university hospital from January 2019 till January 2020.

This study was conducted at the Department of Obstetrics and Gynecology at Beni-Suef University Hospital. The study included 100 pregnant women which were eligible and willing to comply with the study protocol, after informed consent was obtained. The patients received 8 mg of dexamethasone (Epidrone, Epico Egypt) intramuscularly every 12 hours for 48 hours.

Our research included the following parameters:

1. The baseline characteristics:

- Age.
- Gravidity.

- Parity.
- Weight, height, BMI.
- Gestational Age.
- AFI.
- Co-morbidities.

2. Analytical data:

- Fetal Doppler (umbilical artery doppler indices and middle cerebral artery Doppler indices) before administration of dexamethasone and after 12 hours and 24 hours from last dose.
- Neonatal outcome.

The analyzed data were collected and tabulated and the following results were obtained.

Table (1): Impact of dexamethasone on Pulsatility index (PI) of umbilical artery:

Umbilical artery PI	Range	Mean \pm SD	P value
Baseline	0.80-1.4	0.97 \pm 0.17	P1= 0.19
After 12 hours	0.79-1.4	0.95 \pm 0.17	P2= 0.91
After 24 hours	0.79-1.45	0.96 \pm 0.16	P3= 0.39
P1:P-value comparing between baseline (UA) PI and 12 hours(UA)PI.			
P2:P-value comparing between baseline (UA) PI and 24 hours (UA)PI.			
P3:P-value comparing between 12 hours (UA) PI and 24hours (UA)PI.			

Mixed model ANOVA is used to estimate the effect of dexamethasone on umbilical artery PI (repeated measures over time), showing that there are no significant statistical differences across the three time points (**baseline, 12hours and 24 hours**).

Table (2): Impact of dexamethasone on Resistance index (PI) of umbilical artery:

Umbilical artery RI	Range	Mean ±SD	P value
Baseline	0.60-0.85	0.69±0.048	P1= 0.57
After 12 hours	0.65-0.85	0.7±0.05	P2= 0.28
After 24 hours	0.63-0.85	0.7±0.047	P3= 1
P1:P-value comparing between baseline (UA) PI and 12 hours(UA)PI. P2:P-value comparing between baseline (UA) PI and 24 hours (UA)PI. P3:P-value comparing between 12 hours (UA) PI and 24hours (UA)PI.			

Mixed model ANOVA is used to observe the effect of dexamethasone on umbilical artery RI (repeated measures over time), showing that there are no significant statistical differences across the three time points (**baseline, 12hours and 24 hours**).

Table (3): Impact of dexamethasone on pulsatility index (PI) of middle cerebral artery (MCA).

MCA PI	Range	Mean ±SD	P value
Baseline	1.5-2.6	2.09±0.28	P1= 0.49
After 12 hours	1.5-2.7	2.1±0.27	P2= 0.26
After 24 hours	1.5-2.6	2.1±0.26	P3= 0.88
P1:P-value comparing between baseline (MCA) PI and 12 hours(MCA)PI. P2:P-value comparing between baseline (MCA) PI and 24 hours (MCA)PI. P3:P-value comparing between 12 hours (MCA) PI and 24hours (MCA)PI.			

Mixed model ANOVA is used to estimate the effect of dexamethasone on Middle Cerebral Artery PI (repeated measures over time), showing that there are no significant statistical differences across the three time points (**baseline, 12hours and 24 hours**).

Table (4): Impact of dexamethasone on Resistance index (RI) of middle cerebral artery (MCA).

MCA RI	Range	Mean ±SD	P value
Baseline	0.65-0.97	0.84±0.06	P1= 1
After 12 hours	0.62-0.99	0.84±0.06	P2= 0.59
After 24 hours	0.6-0.96	0.83±0.06	P3= 1
P1:P-value comparing between baseline (MCA) RI and 12 hours(MCA)RI. P2:P-value comparing between baseline (MCA) RI and 24 hours (MCA)RI. P3:P-value comparing between 12 hours (MCA) RI and 24hours (MCA)RI.			

Mixed model ANOVA is used to estimate the effect of dexamethasone on Middle Cerebral Artery RI (repeated measures over time), showing that there are no significant statistical differences across the three time points (**baseline, 12hours and 24 hours**).

Table (5): Baseline fetal body weight and birth weight:

	Range	Mean (SD)
Baseline EFW	725 – 1750	1192±293
Birth weight at delivery	850 – 3500	2280±624

Table (6): The gestational age at delivery

		Frequency (%)
Gestational age at delivery	Less than 37 weeks	14(14%)
	More than 37 weeks	86(86%)

Mixed model ANOVA is used to describe and reveal the percent of preterm delivery in cases of IUGR, which was approximately about 14%.

Table (7): Neonatal Outcomes.

		Frequency (%)
Admission to newborn NICU	Yes	24(24%)
	No	76(76%)

This table is used to describe the neonatal outcomes in IUGR after administration of dexamethasone, which revealed that 24% of the neonatal outcomes needed NICU after delivery.

Table (8): Apgar score after 5 minutes.

		Frequency (%)
	Excellent (score 7-10)	87 (87%)
	Moderately depressed (score 4-6)	10 (10%)
Good	Severely depressed (score 1-3)	3 (3%)
Stillbirth		
Neonatal Death		
Enterocolitis		
Respiratory Distress		
Sepsis		
Intracranial Hemorrhage		
Apgar Score after 5 minutes		

This table is used to show the classification of infants according to Apgar score after 5 minutes of delivery, which revealed that “87%” the infants were born with score of 7-10 “excellent”.

4. Discussion:

Prenatal diagnosis of intrauterine growth retardation (IUGR) often leads to premature delivery for fetal distress or maternal medical condition. Most of these cases receive antenatal corticosteroids for enhancement of fetal lung maturation and this is also known to decrease the incidence of intraventricular haemorrhage and enterocolitis (13).

No serious side effects have been reported after administration of corticosteroids during pregnancy, but some studies reported reduction in fetal body movements, fetal breathing movements and heart rate variation after Dexamethasone administration (12).

Evaluation of fetal well-being with Doppler examination of blood flow velocity waveforms after maternal corticosteroid administration is therefore essential to investigate the fetal hemodynamic effects of exogenous corticosteroids. Previous studies showed conflicting results regarding this important subject (12).

Thus, the current study aimed to investigate the effects of dexamethasone exerted on fetal and uteroplacental circulation as measured different Doppler indices of pregnant women complicated by SGA before and after 12 hours and 24 h of Dexamethasone administration. The study of 100 pregnant women aged 30.7 ± 4.7

with gestational age ranged from 24 to 34 weeks showed that:

Regarding Impact of dexamethasone on Pulsatility index (PI) and resistive index (RI) of umbilical artery: There was no statistical significance before and after administration of Dexamethasone (after 12hours and after 24hours. Similarly, (13) (15) 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 during the dexamethasone course (13) (15).

On the other hand, (7) Umbilical artery Doppler indices showed statistically significant reduction 24 h after dexamethasone administration. This is similarly agreed by (9) who found a reduction in the umbilical artery PI within 24 h following antenatal corticosteroid therapy (7) (9).

The variability of results studies suggests that there are other contributing factors that could influence Doppler indices. Further research will be required to identify these variables.

Regarding Impact of dexamethasone on Pulsatility index (PI) and resistive index (RI) of Middle cerebral artery: which was also examined in our study, MCA Doppler indices showed no statistical significance before and after administration of Dexamethasone. These

findings are in agreement with the results of **Senat and Ville and Wijnberger et al.**

However some studies disagree with our results (4) who observed a transient and significant decrease in fetal MCA (PI, RI) after maternal dexamethasone administration (4), also reported by (7).

Strengths of our study are the large sample size compared with most of previous trials. One of the limitations of the current study 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. Also detailed Doppler studies including the maternal uterine artery, fetal MCA, descending aorta and umbilical artery are recommended in further studies.

5. Conclusion and Recommendations

Conclusion:

Dexamethasone treatment was not associated with significant changes in the mean values of the pulsatility, resistive indices or maximum velocity of flow in umbilical artery and fetal middle cerebral artery. Awareness of this drug induced effect might prevent unnecessary iatrogenic delivery of preterm fetuses.

Recommendations:

Further basic research and clinical studies including larger sample sizes or

pregnancies with fetoplacental dysfunction are needed.

6. References:

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