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Effect of Antenatal Betamethasone on Fetal and Uteroplacental Blood Flow Velocity Waveforms in Preterm Pregnancies with Intra Uterine Growth Restriction

Authors
Dr Renu Jain[1], Dr Jyoti Bindal[2]
[1]Assistant Professor, [2]Professor & Head
Department of Obstetrics and Gynaecolgy, Gajra Raja Medical College, Gwalior, M.P, India
Corresponding Author
Dr Renu Jain
Email: *renujain_1979@rediffmail.com*

Abstract

Background: *Antenatal administration of corticosteroids has been recommended as it promotes fetal lung maturation, reduces the incidence and severity of respiratory distress syndrome and other complications. The objective of present study was to study the effect of antenatal betamethasone administration on fetoplacental circulation on Doppler ultrasonography, in preterm pregnancies with fetal growth restriction and the effect of fetoplacental circulation changes on perinatal outcome.*

Material and Methods: *This prospective study was carried out on 80 pregnant women, with gestational age from 28 – 34 weeks, with intrauterine growth restriction. Color Doppler blood flow study of fetal vessels including umbilical artery, middle cerebral artery and ductus venosus as well as both maternal uterine arteries was done, once before and twice after betamethasone administration and a comparative evaluation was done.*

Results: *There was a statistically significant difference between all Doppler indices in umbilical artery, fetal middle cerebral artery and ductus venosus before and 24 hours after maternal betamethasone administration. No significant effect on maternal uterine arteries was observed. Neonates of women who showed an improvement in umbilical artery PI had significantly lesser requirement of assisted resuscitative measures, better Apgar at 1, 5, and 10 min and required lesser admissions to Neonatal Intensive Care Unit, as compared to neonates of women who did not show any decrease in umbilical artery PI.*

Conclusion: *Maternal betamethasone administration significantly affects fetal circulation but not in all cases with IUGR. So, Doppler study done before and one day after betamethasone administration in pregnancies complicated with IUGR can enable us to identify the subgroup of IUGR cases, who are at higher risk of adverse perinatal outcome.*

Keywords: *Intrauterine growth restriction (IUGR), betamethasone, respiratory distress syndrome.*

Introduction

Pregnancies complicated with intrauterine growth restriction roughly constitute 3-10% of all pregnancies.[1] The incidence of IUGR is six times higher in underdeveloped/developing countries. A large number of IUGR infants are seen in the Asian continent, which accounts for approximately 75% of all affected infants.[2]

IUGR is associated with significant perinatal morbidity and mortality rates. The use of Doppler velocimetry in the diagnosis of fetal growth restriction has been recommended as a possible adjunct to techniques such as nonstress testing or biophysical profile.[1]

Pregnancy with early onset IUGR typically presents before 34 weeks of gestation and are at a higher risk of preterm delivery, mostly because of the need for early termination of pregnancy for fetal indication. Antenatal administration of corticosteroids is recommended for fetal lung maturation in threatened preterm birth. It reduces the incidence and severity of respiratory distress syndrome and other complications like necrotizing enterocolitis, intraventricular hemorrhage and neonatal death.[1]

Some studies resulted in a considerable reduction in fetal body and breathing movements and fetal heart rate variation following maternal betamethasone administration. Knowledge of these transient changes is of significant clinical importance as it may prevent iatrogenic delivery because of suspected fetal distress.[3,4]

Despite many pregnancies exposed to corticosteroids, short term effects of maternal steroid administration on fetal circulation are still uncertain. Therefore, evaluation of fetal well being with Doppler examination of blood flow velocity waveforms is essential to investigate the fetal hemodynamic effects of betamethasone administration. Previous studies showed conflicting results. More importantly, beneficial role of these changes in fetoplacental circulation following maternal betamethasone administration, still remains unclear.

Hence we conducted this study to evaluate the effect of maternal betamethasone administration on fetoplacental circulation on Doppler ultrasonography in preterm pregnancies complicated with fetal growth restriction and the effect of fetoplacental circulation changes on perinatal outcome.

Material and Methods

This prospective study was carried out at Department of Obstetrics and Gynaecology, Kamla Raja Hospital, Gwalior (M.P.), during a period of 2 years from Jan 2015 to Dec 2016.

The study included 80 preterm pregnant women complicated with fetal growth restriction, as per the selection criteria mentioned below.

Inclusion Criteria

1. Gestational age between 28 to 36 weeks.
2. Singleton pregnancy.
3. With intrauterine growth restriction detected by clinical examination or on ultrasound.

Exclusion Criteria

1. Multiple pregnancy.
2. Fetal malformations.
3. Severe preeclampsia necessitating immediate delivery.
4. Non reassuring fetal heart rate tracings.
5. Cases where two doses of betamethasone could not be completed.

Detailed history was taken and a systematic general, systemic and obstetric examination was done. Cases with clinically suspected IUGR were subjected to obstetrical ultrasonography for measurement of fetal biometric parameters, estimation of gestational age, amniotic fluid index (AFI), estimated fetal weight (EFW), placental localization and maturity and for detection of any congenital anomaly. All cases were treated with two doses of 12 mg betamethasone, given intramuscularly, 24 hours apart.

Doppler examinations were performed just before betamethasone administration and repeated between 24 to 48 hours (Day 2) and between 72 to 96 hours (Day 4) after 1st dose of betamethasone administration.

The Doppler examinations were done transabdominally with the fetus in a quite state. The Doppler spectrums were recorded during maternal voluntary apnea.

Color Doppler blood flow study included umblical artery (UI), middle cerebral artery (MCA), ductus venosus and right and left maternal uterine arteries

(RUA and LUA). Doppler waveforms were recorded from umbilical artery in the free floating mid portion of the umbilical cord and from the middle cerebral artery in its proximal third. Ductus venosus was identified by following the intra abdominal portion of the umbilical vein. Blood flow velocities were obtained from both maternal uterine arteries just above their crossing with the iliac artery.

Various Doppler indices (S/D ratio, pulsatility index [PI] value and umbilical artery flow pattern) were recorded. Pulsatility index (PI) and S/D ratio values were calculated automatically by the Doppler machine.

Pulsatility index = Systolic peak velocity –End diastolic peak velocity / time averaged maximum velocity; S/D ratio = Systolic peak velocity / diastolic peak velocity

Patients were managed as per protocol for IUGR. Each patient was followed up till delivery and neonatal outcomes were recorded in terms of birth weight, Apgar score at 1, 5 and 10 minutes, need for resuscitative measures, admission to neonatal intensive care unit (NICU) and neonatal mortality.

Primary outcome measured was detection of changes in Doppler indices before and after betamethasone administration. To see the effect of fetoplacental circulation changes on perinatal outcome, perinatal outcome of women who had shown decrease in umbilical artery PI was compared with those who had not shown decrease in umbilical artery PI following betamethasone administration.

Data was analyzed statistically by using paired t-test, Pearson chi-square test and ANOVA.

Results

A total of 80 preterm pregnant women complicated with intrauterine growth restriction admitted in antenatal ward were included in this study. Out of 80 cases, 18 cases were delivered within 72 hours of 1st dose of betamethasone. So on day 4, Doppler examination was performed on 62 undelivered cases.

Table No 1: Maternal characteristics of the patients

Characteristic	
Maternal age (years); mean±SD (Range)	24.37 ± 3.37 (18-35)
Parity; median (Range)	2.05 ± 1.26 (1-5)
Gestational age (weeks +days); mean+SD (Range)	31.57 ± 1.57 (29.6-33)
PIH	38 (47.5%)

Maximum women (78%) were in age group 20-30 years. At the time of admission, 73% cases were at gestational age between 30-34 weeks. 52% cases were primigravida. (Table 1)

Table No 2 Distribution of cases according to umbilical artery blood flow pattern before betamethasone administration (day 0)

Total cases (n=80)	**Umbilical artery blood flow pattern**			
	Forward end diastolic flow (n=55/80)		**AEDF/ REDF (n=25/80)**	
	S/D ≤ 3.5	**S/D>3.5**	**AEDF**	**REDF**
Number of cases	25	30	20	5
Percentage	31.25	37.5	25	6.25

AEDF- Absent end diastolic flow, REDF- Reverse end diastolic flow.

On day 0, the flow velocity waveform in umbilical artery showed forward flow in 55 (68.75%) cases, AEDF in 20(25%) and REDF in 5(6.25%) women.(Table 2)

Table No 3: Effect of betamethasone administration on fetoplacental circulation

Doppler Index	**Change in PI following betamethasone (between day 0 to day 2) (n=80)**			
	Decrease in PI		**No decrease in PI**	
	No of cases	**%**	**No of cases**	**%**
Umbilical Artery PI	58	72.5	22	27.5
Middle cerebral artery PI	66	82.5	14	17.5
Ductus venosus PI	56	70	24	30

58(72.5%) women showed decrease in umbilical artery PI, 82.5% women showed decrease in middle cerebral artery PI and 70% women showed decrease in ductus venosus PI, 24-48 hours after betamethasone administration.(Table 3)

Table No 4 Fetal and uteroplacental Doppler indices before and 24 hour after betamethasone administration

Doppler Indices	Day 0 mean+SD	Day 2 mean+SD	P value
Umbilical Artery PI	1.71 ± .73	1.55 ± 0.75	<.001
Middle cerebral artery PI	1.46 ± .36	1.25 ± 0.34	<.001
Ductus Venosus PI	0.97 ± 0.28	0.88 ± 0.23	<.001
Umbilical Artery S/D	4.05 ± 1.08	3.55 ± 1.46	<.001
Middle cerebral Artery S/D	3.69 ± 1.13	3.35 ± 1.07	<.001
Right uterine artery PI	1.24 ± 0.68	1.20 ± 0.59	>.05
Left uterine artery PI	1.24 ± 0.59	1.23 ± 0.68	>.05

Day 0- before betamethasone administration, Day 2- between 24-48 hours after first dose of betamethasone administration, PI- Pulsatility index

A statistically significant (P<.001) decrease was found in mean PI values of umbilical artery, middle cerebral artery and ductus venosus and in mean S/D ratio of umbilical artery and middle cerebral artery, between day 0 and day 2 following betamethasone administration. No significant changes were observed in maternal uterine arteries. (Table 4)

Table No. 5: Comparison of umbilical artery and MCA PI and S/D ratio before (Day 0) and after (Day 2 and Day 4) betamethsone in undelivered 62 cases

Doppler index	Day 0 (mean±SD)	Day 2 (mean±SD)	Day 4 (mean±SD)	P value		
				0/2	2/4	0/4
U.A. PI	1.56±0.62	1.31±0.56	1.46±0.61	<.001(S)	<.001(S)	<.05 (S)
U.A. S/D	3.91±1.3	3.43±1.31	3.65±1.38	<.001(S)	<.001(S)	<.05 (S)
MCA PI	1.46±0.37	1.28±0.36	1.38±0.41	<.001(S)	<.001(S)	>.05 (NS)
MCA S/D	3.91±1.13	3.56±1.08	3.79±1.07	<.001(S)	<.001(S)	>.05 (NS)

p 0/2- between day 0 and day 2 value, p 2/4- between day 2 and day 4 value, p 0/4- between day 0 and day 4 value, S-significant, NS- not significant.

On statistical analysis, a significant increase in umbilical artery mean PI and mean S/D ratio, from day 2 to day 4 was observed (p<.001). It was observed that, inspite of this rise in umbilical artery mean PI and mean S/D ratio, values on day 4 remained lower than values of day 0. The difference in umbilical artery mean PI and mean S/D ratio between day 0 and day 4 were statistically significant (p<.05). A statistically significant rise in MCA mean PI and mean S/D ratio between day 2 to day 4 was observed (p<.001), making the difference in mean PI and mean S/D ratio values between day 0 and day 4 insignificant(p>.05). (Table 5)

Table No 6. Umbilical artery flow pattern before and after betamethasone in cases with absent and reversed end diastolic flow in umbilical artery

	Day 0	Day 2	Day 4 (9 cases)	P value		
				0/2	2/4	0/4
Umbilical artery blood flow pattern (no of cases/ total cases)	AEDF (20/80)	FEDF (15) AEDF(5)	FEDF (4) AEDF(5)	<.05	>.05	>.05
	REDF (5/80)	FEDF(1) AEDF(1) REDF(3)	-	>.05	-	-

AEDF- Absent end diastolic flow, REDF- reverse end diastolic flow, FEDF- Forward end diastolic flow in umbilical artery.

24 - 48 hours after first dose of betamethasone, in 20 fetuses with AEDF on day 0, the flow velocity waveform in umbilical artery, changed to forward diastolic flow in 15 cases.11 cases delivered within 72 hours of first dose of betamethasone. On day 4 doppler study (was done in remaining 9

cases), in 4 cases forward flow was maintained, while in rest of 5 cases blood flow pattern returned to AEDF. Changes in flow pattern of umbilical artery between day 0 and day 2 and day 2 to day 4 was statistically significant. (p<.05)

24 – 48 hours after first dose of betamethasone on day 2, in fetuses with REDF on day 0, the flow velocity waveform in umbilical artery, changed to forward diastolic flow or AEDF in 2 patients and 3 patients had persistent REDF. This change was statistically insignificant. All cases with REDF delivered within 72 hours of 1st dose of betamethasone. (Table 6).

Table no 7: comparison of mode of delivery

Mode of delivery (n=80)	Group A Reduction in UA PI (n=58)		Group B No reduction in UA PI (n=22)		P value
	No of cases	%	No of cases	%	
Vaginal	35	60.3	15	68.1	>.05 (NS)
LSCS	23	39.65	7	31.8	

UA-Umbilical artery, LSCS- lower segment caesarean section, PI- pulsatility index

In group A, 60.3% women and in group B, 68.1% women delivered vaginally. In group A, 39.65% women and in group B, 31.8 % women were delivered by LSCS. This difference in mode of delivery was statistically not significant (p>.05). (Table 7)

Table No 8: Comparison of perinatal outcome

Perinatal outcome (n=80)	Group A Reduction in UA PI (n=58)		Group B No reduction in UA PI (n=22)		P value
	No of cases	%	No of cases	%	
Live	55	94.8	16	72.72	<.05(S)
IUD	3	5.17	6	27.27	
NICU admission	23	39.66	8	36.36	>.05(NS)
Neonatal mortality	2	3.44	2	9.09	>.05 (NS)
Birth weight (gm) mean+SD (Range	1491±398 (700-2225)		1320±470 (760-2100)		>.05 (NS)

IUD- Intrauterine death, NICU-Neonatal intensive care unit

Significantly more intrauterine deaths occurred among women who did not show any reduction in umbilical artery PI (group B), compared to women who showed reduction in umbilical artery PI (group A) (p<.05). Mean birth weight was higher in group A as compared to group B, but this difference was statistically insignificant. (Table 8)

Discussion

Abnormal fetoplacental circulation plays an important role in causation of fetal growth restriction. It has been reported that betamethasone alters fetoplacental vascular resistance. This study evaluate the effect of betamethasone on fetoplacental and uterine circulation in preterm pregnancies complicated with IUGR and effect of these changes on perinatal outcome.

In present study, gestational age ranged from 29.6weeks to 33 weeks, with a mean gestational age of 31.57 ± 1.57 weeks. In study by Robertson et al, mean gestational age at the time of admission was 30.8 weeks.[5]

Several investigators have studied Doppler flow velocity patterns in the human fetus after antenatal corticosteroid administration. In present study, significant reduction in the mean pulsatility index, mean systolic/ diastolic ratio of the umbilical artery were found between 24-48 hours after 1st dose of maternal betamethasone administration, suggesting improvement in blood flow pattern of umbilical artery. We found that reduction in umbilical artery PI and S/D ratio were maintained

till day 4 (72-96 hours), after 1st dose of betamethasone, with a significant difference in values when compared with their respective day 0 values. Improvement (decrease) in umbilical artery PI was observed in 58 (72.5%) cases, while 22 (27.5 %) cases did not show any improvement. Nozaki et al, also reported significant difference in mean UA-PI value after corticosteroid administration, but they observed no significant changes in MCA Doppler.[6]

In present study, out of 25 cases of severe IUGR with AEDF or REDF at admission, 17 (68%) patients showed an improvement in umbilical artery blood flow patterns, while 8 (%) cases had persistent AEDF or REDF following betamethasone administration. These results were similar to the results reported by Nozaki et al, who found a reduction in UA-PI in 90.6% cases, with return of EDF in 68.7% cases.[6] In study by Robertson et al, betamethasone administration was associated with a transient return of end diastolic umbilical artery flow in 58 pregnancies.[5] Piazze et al, reported significant persistent return of umbilical artery EDF in 21 cases out of 64 cases of IUGR with REDF or AEDF.[7] It seems that pregnancies with umbilical AEDF, that do not show a transient return in EDF have lost the ability to explore a vascular response to corticosteroids due to severe placental insufficiency.

Contrary to these studies, no changes in fetal Doppler waveform patterns of the UA, MCA and DV were reported by Wijnberger et al in severely IUGR fetuses and Deren O et al in healthy preterm fetuses.[8, 9]

In present study, mean MCA PI values showed a significant reduction between day 0 and day 2, followed by an increase between day 2 to day 4 following betamethasone administration. So we found that betamethasone administration was associated with a significant but transient reduction in MCA PI and S/D ratio. It is possible that changes in the MCA PI are a result of fetal cerebral blood flow redistribution. It has been postulated that fetal brain is very sensitive to over perfusion or changes in the pressure and it is efficiently protected through autoregulation of cerebral blood circulation, which might explain our findings. Urban et al, Atalay Ekin et al, and Elwani et al, also reported significant decrease in PI value of MCA following corticosteroid administration.[10,11,12] In study by Thuring et al, no significant effect of betamethasone was observed in fetal middle cerebral artery.[13]

Present study also included Doppler examination of ductus venosus. A significant decrease in ductus venosus mean PI was noted on day 2 (between 24 -48 hours) following betamethasone administration. Similar results were reported by Nozaki et al and Thuring et al.[6, 13] Our results differ from Ekin et al, who reported no significant difference in ductus venosus PI, before and after antenatal corticosteroid treatment.[11]

In present study, the maternal uterine arteries PI did not show any significant change following betamethasone administration. Similar finding was reported in other studies.[11,12] Contrary to our study, Elwani et al, reported a significant difference in uterine artery PI, before and 24 hour after betamethasone.[12]

We correlated the findings of umbilical artery changes following betamethasone administration with the perinatal outcome, to note whether these changes in fetoplacental circulation following corticosteroid administration are beneficial or harmful to the IUGR fetuses. In present study, we found that the perinatal outcome of 58 women who had a decrease in umbilical artery PI (group A) was better than the perinatal outcome of 22 women who did not show decrease in umbilical artery PI (group B), following betamethasone administration. Neonates in group A had better Apgar scores at 1 and 5 min, required less ventilator support, required less admission in neonatal intensive care unit and had less complications like respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis or hyperbilirubinemia as compared to neonates in group B. Robertson et al, found significantly higher levels of respiratory distress

syndrome, chronic lung disease, and need for ventilation in 29 fetuses with no return of UAEDF post corticosteroid treatment vs. 49 fetuses with return of UAEDF.[5] Piazze et al, in their study of 64 IUGR fetuses, reported a 67% RDS rate with persistent AEDF and REDF after steroid administration and only a 20% rate if UAEDF returned.[7]

The current hypothesis is that fetuses with umbilical artery end diastolic flow (UAEDF) that show a transient return, have sufficiently intact physiological mechanisms to respond to corticosteroid challenge, while those with persistent UAEDF are a group with greater preexisting compromise.

Intrauterine deaths and perinatal mortality were found to be significantly higher in group B as compared to group A. Robertson et al also reported similar finding in their study.[5]

Accepting that the observed Doppler changes in fetoplacental circulation are betamethasone induced, these findings are of value in the assessment of fetal surveillance of pregnancies complicated by IUGR following betamethasone administration. In these cases of IUGR with severely impaired fetoplacental flow, Doppler examinations of fetal circulation for fetal surveillance should be done before the administration of betamethasone because Doppler findings after betamethasone administration may be falsely reassuring and delivery of compromised fetuses would be delayed.

Conclusion

Maternal antenatal betamethasone treatment caused a significant transient change in blood velocity waveforms and decrease in PI in the umbilical artery, middle cerebral artery and ductus venosus, but did not have any effect on uteroplacental circulation, suggesting a direct effect of corticosteroids on fetoplacental circulation.

Maternal betamethasone administration significantly affects fetal circulation but not in all cases with IUGR. So, Doppler study done before and one day after betamehasone administration in pregnancies complicated with IUGR can enable us to identify the subgroup of IUGR cases who are at higher risk of adverse perinatal outcome.

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