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Study of Cerebro-Placental Ratio in Pregnancies with Abnormal Umbilical Artery Doppler in Predicting Adverse Perinatal Outcome: Are we here yet?

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Abstract

Objective: To evaluate the effect of abnormal Umbilical artery Doppler and Cerebro-placental ratio on perinatal outcome in pregnant women between 28-40 weeks of gestation.

Methods: It's a prospective observational study of 139 pregnant women with abnormal umbilical artery Doppler and cerebro-placental ratio from 28-40wks excluding all medical diseases. Doppler was considered abnormal when pulsatality Index (PI) > 95th percentile for gestational age and when Cerebro-placental Ratio is less than 1.08.

Results: Abnormal Doppler results are grouped into 3 groups, AEDF (absent end diastolic factor), REDF (reverse end diastolic factor), CPR (cerebro-placental ratio) <1. In AEDF, REDF, CPR groups, respiratory distress syndrome (RDS) was noted in73%, 95%, 37%. Low Apgar (score less than 7), was 4.5%, 35%, 3.1%.FGR was noted in 37%, 81%, 15%.

Birth weight < 2.5kg as seen in 32%, 45% whereas in REDF group 95% of babies were <2kg.Sepsis were noted more in REDF 70% whereas none in CPR group. Meconium stained amniotic fluid seen in 13%, 10% and none in CPR group. All babies required NICU stay more than 7 days in REDFcompared to other groups. Perinatal mortality was highest in the REDF (15 %) compared to AEDF (2.29 %) and CPR <1.08 (Zero) [p <0.001].

Conclusion: Abnormal umbilical artery Doppler along with CPR <1 is associated with substantial risk of adverse perinatal outcomes. Abnormal CPR and AEDF are not the indications for immediate delivery. Using Dopplers of other vessels like ductus venosus with UA- AEDF could help in deciding the time of delivery and reduce the adverse perinatal outcome.

Keywords: Absent end diastolic flow; Cerebro-placental ratio; Fetal growth restriction; Perinatal outcome; Reversal of end diastolic flow; Umbilical artery Doppler

Introduction

In clinical practice, the most frequently used method to identify fetal circulation is Doppler velocimetry, as it is non-invasive method for assessment of fetal-placental circulations [1]. Middle cerebral and umbilical artery Doppler shows the evidence about placental resistance and the variations in hemodynamic of fetus in reaction to it. Umbilical artery Doppler replicates the abnormal development of the placental tertiary stem villi which rises the placental resistance [2,3].

Cerebro-placental ratio is the ratio (CPR) of the MCA to UA Doppler, compare the resistance to blood flow in the umbilical artery and the MCA. It quantifies the part of flow delivering to the brain and the placenta. (CPR is normal if it >1). In redistribution of blood flow to the brain CPR becomes < 1. [3,4].

The purpose of present study was to evaluate the effect of Doppler abnormalities in Umbilical artery and cerebro-placental ratio on perinatal outcome, the time duration taken for the normal Doppler to become abnormal and various maternal factors contributing for these Doppler changes.

Methods

The study was a prospective observational study of pregnancies between 28-40 weeks of gestation when Doppler study showed abnormal results. Pregnant women with singleton gestation attending for routine antenatal care in OBG department between August 2017 to July 2019 were recruited, if the umbilical artery Doppler PI was > 95th centile for the gestational age or CPR was less than 1.08. Exclusion criteria were fetal structural and/

or chromosomal abnormalities. The Ethics committee approval taken (Registration no.: ECR/146/Inst/KA/2013; Project approval no. IEC- 532/2017). The waveform analysis of umbilical artery and middle cerebral artery done. A free floating loop of umbilical cord. The angle of insonation was then optimized and the signals obtained.

Umbilical artery PI was considered elevated when it was more than 95th percentile

• Middle cerebral artery: The largest terminal branch of internal carotid artery. It was insonated at the level of greater wing of sphenoid. The angle of insonation can be easily kept at 0 for this vessel. Systolic flow (A) and the diastolic flow (B) for the above mentioned arteries were obtained. Doppler indices were calculated- Pulsatality index= A-B/ mean. Further management of the cases were decided depending on the clinical status of the patients and the Doppler report, and pregnancies were terminated as and when indicated.

Patients who continued pregnancy after the Doppler examination, Doppler was repeated as and when the treating obstetrician decided depending on the worsening of the condition. The decision of termination of pregnancy was taken as per the consultant at various stages of Doppler flow velocimetry abnormalities.

Mode of delivery was decided depending on the clinical condition of patients and the indications. At the time of delivery details such as baby weight, Apgar score, meconium staining of liquor and neonatal intensive care unit admissions were noted and were followed up for the outcome.

Statistical analysis

Sample size and power calculations were performed based on the prevalence of the condition at the hospital. Statistical analysis was performed using SPSS version 22.0.

ANOVA: Analysis of variance (ANOVA) is a statistical technique that is used to check if the means of two or more groups are significantly different from each other. ANOVA checks the impact of one or more factors by comparing the means of different samples.

t- Test: Two sample assuming equal variances: The t statistic to test whether the means are different can be calculated by the unbiased estimators of the variances of the two samples. The denominator of t is the standard error of the difference between two means.

Differences between groups were deemed significant only if two-tailed P was <0.01

Results

A total of 176 women consented to participate in the study, 12 were excluded as they had pseudo normalization of Doppler. Out of 164 patients, 25 patients were excluded as they underwent LSCS due to other indications like anhydramnios, Imminent eclampsia, fetal distress, non-reassuring NST. 139 patients were included in the study whose pregnancy was intervened solely on the basis of Doppler abnormalities. Demographic characteristics are summarized in Table 1. Mean age of the studied patients was 28.89 years (SD- 4.54 years). Nulliparous women represented 64.75%.

Characteristic	Median (range) or number (%)
Maternal age at delivery (years)	28.89 (21- 43)
Parity	
Nulliparous	90 (64.75%)
Multiparous	49 (35.25%)
Maternal Complications	
Hypertensive disorders of pregnancy	69 (86.25%)
Gestational diabetes	1 (1.25%)
Both HTN and GDM	10 (12.5%)
Mode of Delivery	
Caesarean delivery	136 (97.84%)
Vaginal delivery	3 (2.16%)

Table 1: Demographic characteristics of study population.

Gestational age at presentation ranged from 28 weeks to 37 weeks 3 days. Hypertensive disorders of pregnancy were noted in 86.25%, Gestational diabetes mellitus was noted in 1.25% and both HTN and GDM was found in 12.5%. Caesarean section was the most common mode of delivery. Out of 32 patients with CP ratio <1.08 only 3 underwent induced vaginal delivery and 29 underwent LSCS. All patients with absent and reversal of end diastolic flow velocity underwent LSCS. In CP ratio less than 1.08 group, none delivered between 28-32 weeks, 28.125 % delivered between 32-36 weeks.

Only 27.58% delivered in AEDF group but 75% delivered in REDF group between 28-32 weeks. Numbers of patients delivered between 32- 36 weeks were 55.18% and 25% in AEDF and REDF group respectively. In gestational more than 36 weeks, 14% in CPR< 1.08 and 17.24% in AEDF group, none in REDF group as shown in Figure 1.

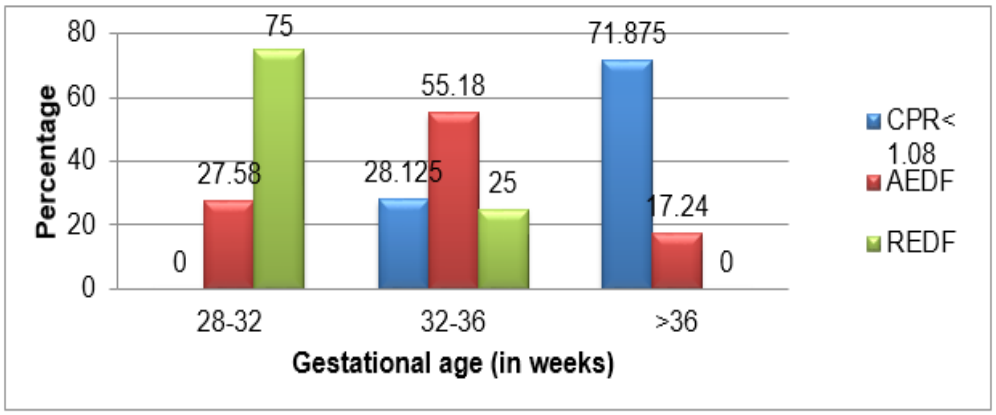

Figure 1: Gestational age at delivery and the corresponding abnormal UA Doppler findings.

Out of 139 patients, all progressed from Umbilical artery PI > 95th (CPR>1.08) to CPR<1.08, among them 32 were delivered when they had CPR< 1.08. Remaining 107 progressed to AEDF, out of them 87 patients were delivered when they had AEDF. Remaining 20 patients progressed to REDF and then were delivered. The number of days taken for progression from UA PI >95th centile (CPR>1.08) to CPR<1.08, CPR<1.08 to AEDF and AEDF to REDF was 6.52 days (SD- 3.75), 13.25 days (SD- 9.39) and 6.63 days (SD- 3.86) respectively.

In Patients with CP ratio < 1.08, 50% of babies weighed between 2- 2.5 kg followed by 40.63% between 1.5 to 2 kg. Babies weighing between 1.5 to 2 kg were 32.18% in AEDF group and none in REDF cases whereas babies weighing between 1- 1.5 kg in AEDF group was 45.9% and REDF was 35%, between 500 g to 1 kg in AEDF group were 17.24 %and 65% in REDF group. The Table 2 signifies that babies born with REDF was below 1.5 kg (Severe FGR).

Doppler velocimetry	Birth weight									
	0.5-1 Kg		1- 1.5 Kg		1.5- 2 Kg		2- 2.5 Kg		>2.5 Kg	
	No.	%	No.	%	No.	%	No.	%	No.	%
CPR <1.08	0	0	0	0	13	40.63	16	50	3	9.37
AEDF	15	17.24	40	45.98	28	32.18	4	4.60	0	0
REDF	13	65	7	35	0	0	0	0	0	0

Table 2: Doppler and birth weight.

Table 3 shows that sepsis in CPR<1.08 was zero, 43.67% in AEDF group and 70% in REDF group with significant difference. Apgar at 5 minute less than 7 was only 3.125% in CPR<1.08 group, 4.59% in AEDF group and 35% in REDF group, there was not significant difference between CPR<1.08 and AEDF group, but was significant between AEDF and REDF group (p value <0.001). Incidence of RDS was 31.25% in CPR< 1.08, 48.27% in AEDF and 95% in REDF group with significant difference. Only 5% in REDF had Intraventricular hemorrhage and zero in CPR<1.08 and AEDF group.

Fetal Outcome	CPR< 1.08 (N=32)		AEDF (N= 87)		REDF (N=20)		P value between CPR<1.08 and AEDF	P value between AEDF and REDF
	No. of patients	%	No. Of patients	%	No. of patients	%		
Sepsis	0	0	38	43.67	14	70	<0.001	0.033

APGAR at 5 min < 7	1	3.125	4	4.59	7	35	0.725	<0.001
RDS	10	31.25	42	48.27	19	95	0.0011	0.0013
IVH	0	0	0	0	1	5	NA	0.04
NICU stay > 7days	20	62.5	80	91.95	20	100	<0.001	0.198
NND	0	0	2	2.29	3	15	0.39	0.015
MSAF	0	0	12	13.79	2	10	0.02	0.653
FGR	12	37.5	71	81.60	19	95	< 0.001	0.14

Table 3: CPR< 1.08, AEDF and REDF and their effect on perinatal outcome.

All neonates in REDF group required NICU stay for more than 7 days, in AEDF group 91.95% and CPR< 1.08 was 62.5%, significant difference was found between CPR<1.08 and AEDF group but not between AEDF and REDF group. Incidence of neonatal death was significantly increased in REDF group compared to AEDF group. Significant fetal growth restriction was noted between CPR<1.08 and AEDF group but not between AEDF and REDF group (Figure 2-5).

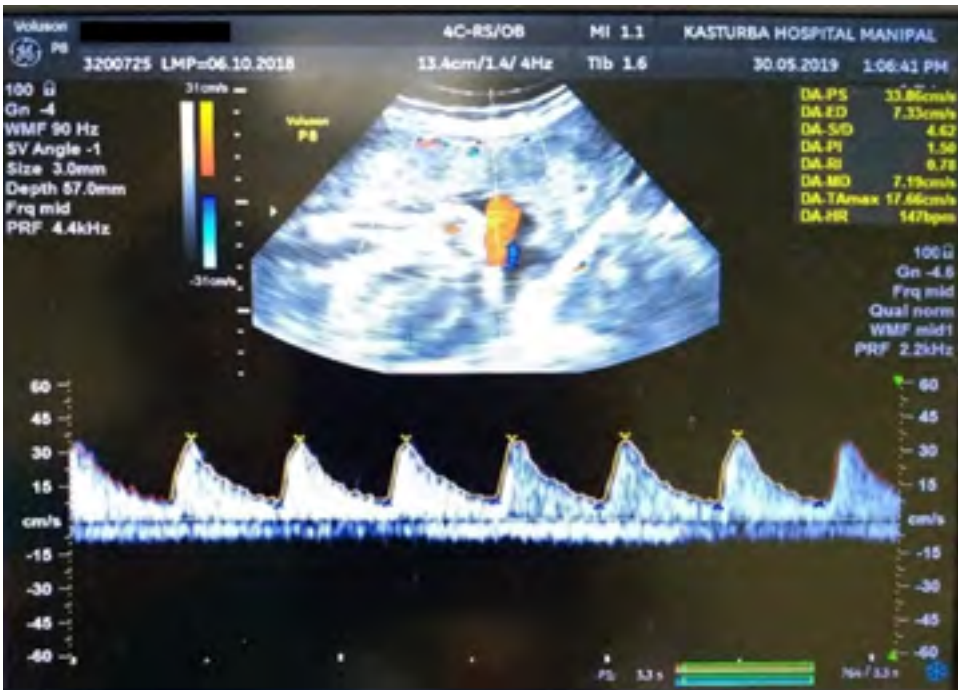

Figure 2: Increased resistance in umbilical artery.

Figure 3: Absent end diastolic flow in umbilical artery.

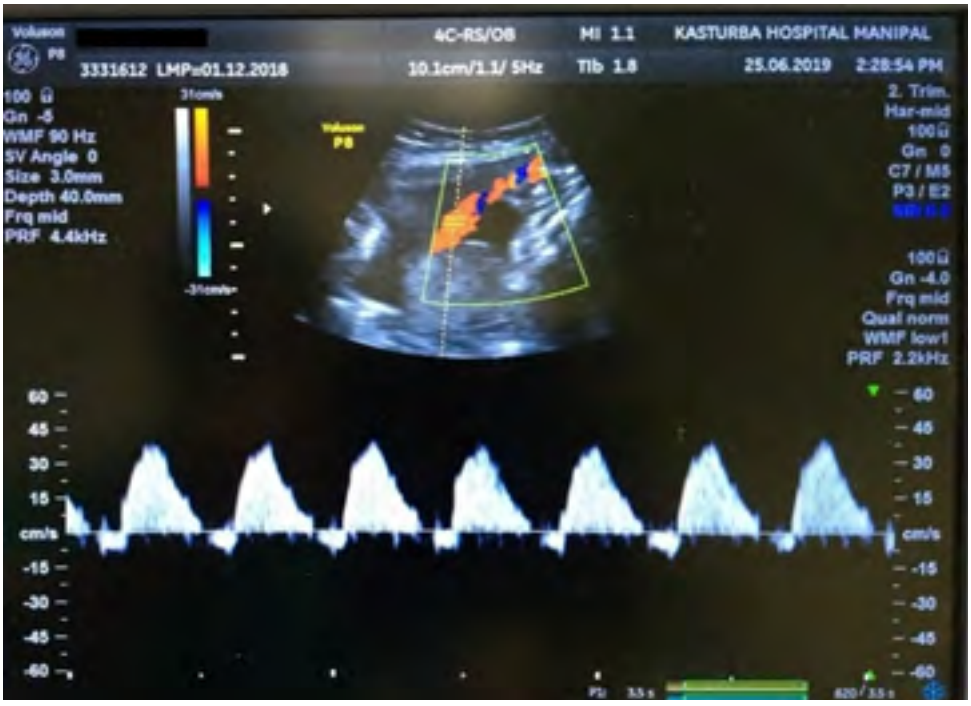

Figure 4: Reversed end diastolic flow in umbilical artery.

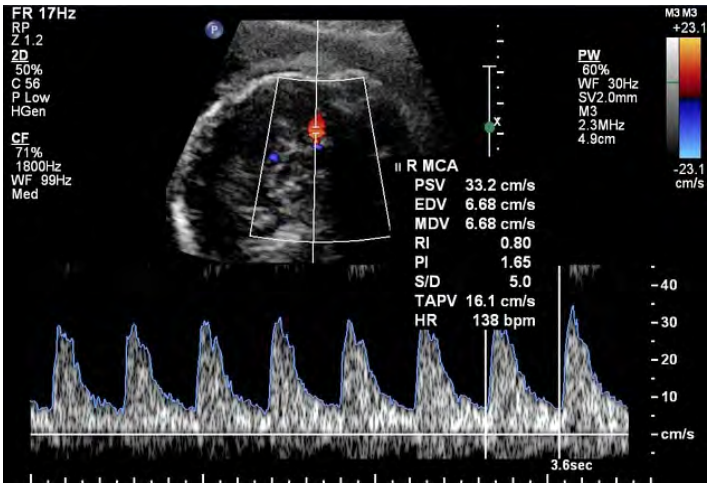

Figure 5: Middle cerebral artery Doppler.

Discussion

In the study of uteroplacental flow, the role of Doppler ultrasound is well known. The prediction of fetal outcome and placental pathology is also well identified by the Doppler study. The connotation between perinatal outcome and Doppler waveform velocities have been studied by various studies that have been conducted over the years.

Evidence suggests that umbilical artery Doppler studies which shows the upsurge in peripheral vascular resistance, is reliable with the placental vascular variation [1,2]. To the extent that fetal blood vessels are concerned in cases of intrauterine growth restriction, they are intricated by hypoxemia, vascular resistance rises in utmost somatic blood vessels like iliac, aorta, renal arteries, and diminutions in cerebral blood vessels like middle cerebral artery, internal carotid. This is supposed to reproduce replacement of the circulation to withstand sufficient oxygen supply to the vital structures like cardiovascular system and neuronal system [3].

Various biographers have suggested that Doppler velocimetric studies should be utilized to screen intrauterine growth restriction fetuses. Doppler practice can be used as supplementary level assessment in growth restricted fetuses to identify fetal hypoxia [4].

In the present study, 87 cases of AEDF of umbilical artery Doppler, all cases were of high-risk pregnancy group. The fore mentioned statement is in covenant with several other studies [5-7]: they specifically distinguished AEDF during pregnancies that were of high risk group, either with hypertensive disorders of pregnancy or intra uterine growth restriction. In such cases, for prediction of fetal distress, the supreme investigation is the umbilical artery Doppler flow study and is identified earlier than antenatal monitoring of fetal heart rate. The analytical assessment is effective in the pregnancies with high risk, and not revealed in the entire antenatal population.

Finding Absence of End Diastolic Flow (AEDF) is always an apprehensive sign: the present study illustrated a mortality rate of 2.29 % (2/87), prematurity (<36 weeks of gestation) in 82.76% of cases, SGA (10th centile) in 81.60 %, and all underwent emergency LSCS. Neonatal morbidity was significant. Tyrrell S and Brar HS [8,9] recognized caesarean rate for fetal distress in 38-78%, 53% had mortality. Mortality rate increased to 90% in patients with reversal of end diastolic flow velocity. AEDF compels hospitalization and thorough monitoring of fetus.

When the question arises as regarding timing of delivery, the following things were noted. In a small number of cases (16/87) the study distinguished an interval between identification of AEDF and delivery greater than 2 to 3 weeks. Several biographers [5-9] have established eleven weeks between the arrival of absent end diastolic flow and sign of fetal distress but the median test-to-delivery interlude is constantly small: four days according to Divon et al. [10], 6.63 days according to present study.

AEDF is constantly an indication of fetal distress for Brar and Platt [9], leading to thorough fetal monitoring, and is not sufficient enough for delivery as there can be improvement during antepartum period. Some cases showed reappearance of diastolic flow with bed rest. Nicolaides et al. [11], performed cordocentesis in fifty nine cases of absent EDF for studying pH and oxygen tension, normal results were noted in seven fetuses, hypoxia in twenty five, low pH was noted in five and twenty two with both. Choosing the time of delivery necessitates appreciation of these altered situations. Divon et al [10]. practiced the subsequent standards as suggestions for delivery: (i) deterioration of maternal ailment, (ii) oligohydramnios (single deepest vertical pocket <2 cm), (iii) biophysical profile score ≤ 4, (iv) severe FGR (3rd centile) with proven maturity of lungs. Present study showed that pregnancy can be continued after detection of AEDF without significant perinatal mortality. However timing of delivery varies among each pregnancies.

P. Poulain and colleagues [12] in retrospect studied consequence of pregnancy in sixty two cases with AEDF of umbilical artery. Almost all pregnancies belonged to high risk group. Several cases had either uterine (55.5%) or cerebral (65%) Doppler flow aberrations, or both (38%). They noted forty four (71%) live-births, an increased caesarean rate (86%), prematurity (< 37 weeks of POG) (75%), and small for gestational age (39%). APGAR score <7 at 1 minute was noted in 45% of neonates, which fell to 27% at 5 minutes. The mortality rate in neonates was 6.9% and the overall perinatal mortality rate was thirty four percent (21/62). Morbidity was substantial (severe morbidity was noted in seven cases, chromosomal abnormality with poor prognosis was noted in 2 cases).

F.D. Johnstone et al [13] studied that AEDF in the umbilical artery is consistently allied with atypical pregnancy. Delivery of fetus within few days of identifying AEDF is by other evidence of fetal compromise, but in most cases the interval of anomalous Doppler flow pattern could not be identified. AEDF in the umbilical artery gives the impression of being an established problem, as twenty two out of twenty four neonates weighed less than the 5th percentile and one other was the baby of an uncontrolled diabetic. They found that maximum pregnancies with AEDF will progress to abnormal patterns of fetal heart rate, and abnormal Doppler velocimetry lead unusual cardio-tocography by up to twenty four days. Eliminating the only case of stillbirth, merely 3 women delivered vaginally, and out of these, one baby was delivered severely asphyxiated although preparations for caesarean section were being arranged. The present study noted 100% caesarean section for AEDF fetuses. It is therefore flawless that the inference of AEDF in the umbilical artery specifies significantly high-risk pregnancy necessitating rigorous monitoring of the fetus, as remote case reports have formerly recommended [14,15].

Mandruzzato. G. P et al studied thirty-two fetuses with AEDF OR REDF in umbilical artery and/ or descending aorta of fetus. AEDF was noted in 21 cases and reversal in 11 cases [16]. No significant variance was noted in mean gestational age at delivery. But significant difference was noted in mean weight at birth and perinatal mortality rate. No perinatal mortality was noted in AEDF group whereas 63.6% perinatal mortality was noted in REDF group. In the present study, AEDF group had 2.29% and REDF had 15% perinatal mortality rate. The appearance of fetal distress is always preceded by absent end diastolic flow.

Reversal of end diastolic flow single-handedly does not appear to be the utmost sensitive sign of impending fetal demise in those cases, as different time durations from identification of reversal of end diastolic flow to delivery with survival have been informed in the collected works. Zelop et al. [17] testified a period of 3.6 ± 1.5 days with 33.3% of perinatal mortality, Brar and Platt described 4.2 ± 1.4 days and perinatal mortality of 50% and Wang et al. [18] reported 10 ± 8.2 h and neonatal mortality of 50%. The mean age at delivery was 29.1 ± 0.6, 30.1 ± 2.5 and 31.8 ± 3.2 gestational weeks, respectively. Kurkinen-Raty et al. stated average of 1 (range, 1-21) day with a 33.3% perinatal mortality and average gestational age of 31.2 ± 2.4 gestational weeks. Zelop et al. [17] had a maximum time from diagnosis to delivery with survival of 18 days. But, Wang et al. [19] delivered within hours, but still had the highest mortality of 50% among neonates Venous Doppler was not done in any of these studies. In a study done by Arduini et al. [20] time period amid the incidence of AED frequencies and late heart rate decelerations during antepartum period was evaluated. This time interval was different significantly between fetuses, and was mostly dependent on presence of maternal hypertension, venous pulsations and gestational age. These assessments are fetal cardio-tocography, biophysical ultrasound score and maternal uterine and fetal cerebral vessels Doppler study. This intensive care pooled with the practice of recognized conditions for delivery is the solitary method to advance the neonatal prognosis.

Limitation of the Study

Estimation of Doppler indices was not done by a single obstetrician and thus there might be inter-observer variation. However, all estimations were made by senior obstetric sonologists with experience in obstetric ultrasound. The machine and software used for estimation remains constant for all women. The results of the study may not be applied to other centres, especially if they don't have the dedicated obstetric ultrasound centre where obstetricians perform the antenatal ultrasound examinations.

Conclusion

Umbilical artery Doppler velocimetry can be used as a predictor of perinatal outcome in high risk pregnancies like hypertensive disorders of pregnancy, fetal growth restriction. The present study cerebroplacental ratio less than 1.08 had no perinatal mortality and least perinatal morbidity. Hence pregnancies need not be terminated with CPR <1.08. The time interval from initial detection of UA- AREDF to delivery is highly variable, and it is reasonable to manage high risk groups like growth-restricted fetuses and hypertensive pregnancies with UA-AEDF expectantly with careful surveillance for fetal well-being to prolong the gestational age and promote fetal maturation.

This study has a strong correlation that pregnancies need not be terminated at absent end diastolic flow in umbilical artery. However, comparatively termination of pregnancy at reversal of end diastolic flow had poor perinatal outcome with the confounding factor being most deliveries were at very preterm gestation (28-32 weeks) and extremely low birth weight. In AEDF cases other than where fetal anomalies are excluded or fetal lung maturity is achieved; explore norms to defer the immediate delivery.

Further research is necessary regarding other Doppler flow velocimetric changes like ductus venosus that may help in deciding prolongation of pregnancy beyond absent end diastolic flow with less adverse effects on perinatal outcome, a balance between preventing very preterm delivery and perinatal mortality. These findings suggest that the prognosis of fetuses with UA-AREDF is not as poor as many believe, and proper decision-making regarding the timing of delivery may contribute to favorable outcomes.

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References

1. Giles WB, Trudinger BJ, Baird PJ (1985) Fetal umbilical artery flow velocity waveforms and placental resistance: pathological correlation. Br J Obstet. Gynaecol 92: 31-38.
2. Fok R, Pavlova Z, Benirschke K, Paul R, Platt LD (1990) The correlation of arterial lesions with umbiluical artery flow velocity in the placentas of small for dates pregnancies. Obstet Gynecol 75: 578-583.
3. Mandruzzato GP, Bogatti P, Veglio PC, Rustja D, Casaccia R, et al. (1990) fetal haemodynamic adaptation to intrauterine growth retardation. Fetal Autonomy and Adaptation 165-174.
4. Marsal K, Persson P (1988) Ultrasound measurement of fetal blood velocity waveforms as a secondary diagnostic test in screening for intrauterine growth retardation. J clin Ultrasound 16: 239-244.
5. Johnstone FD, Haddad NG, Hoskins P, McDicken W, Chambers S, et al. (1988) Umbilical artery doppler flow velocity waveform: the outcome of pregnancies with absent end diastolic flow. Eur J Obstet Gynecol Reprod Biol 28: 171-178.
6. Trudinger BJ, Ishikawa K (1990) Use of Doppler ultrasound in the high-risk pregnancy. Clin Diagn Ultrasound 26: I l9- 137.
7. Rochelson B, Schulman H, Farmakides G, Bracero L, Ducey J, et al. (1987) The significance of absent end-diastolic velocity in umbilical artery velocity waveforms. Am J Obstet Gynecol 156: 1213-1218.
8. Tyrrell S, Obaid AH, Lilford RJ (1989) Umbilical artery Doppler velocimetry as a predictor of fetal hypoxia and acidosis at birth. Obstet Gynecol 74: 332-337.
9. Brar HS, Platt LD (1988) Reverse end diastolic flow velocity on umbilical artery velocimetry in high risk pregnancies: an ominous tinding with adverse pregnancy outcome. Am J Obstet Gynecol 159: 559-562.
10. Divon MY, Girz BA, Lieblich R, Langer o (1989) Clinical management of the fetus with markedly diminished umbilical artery end diastolic flow. Am J Obstet Gynecol 161: 1523-1527.
11. Nicolaides KH, Bilardo CM, Soothill PW, Campbell S (1988) Absence of end diastolic frequencies in umbilical artery: a sign of fetal hypoxia and acidosis. Br Med J 297: 1026-1027.
12. Poulain P, Palari JC, Milon J, Betremieux P, Proudhon JF, et al. (1994) Giraud. Absent end diastolic flow of umbilical artery Doppler: pregnancy outcome in 62 cases. European Journal of Obstetrics & Gynecology and Reproductive Biology 53:115-119.
13. Johnstone FD, Haddad NG, Hoskins P, McDicken W, Chambers Set et al. (1988) Umbilical artery doppler flow velocity waveform: the outcome of pregnancies with absent end diastolic flow. European Journal of Obstetrics & Gynecology and Reproductive Biology 28: 171-178.
14. Erskine FLA, Ritchie JWK (1985) Umbilical artery blood flow characteristics in normal and growth retarded fetuses. Br J Obstet Gynaecol 92: 605-610.
15. Trudinger BJ, Giles WB, Cook C, Bombardieri J, Collin SL (1985) Fetal umbilical artery flow velocity waveforms and placental resistance: clinical significance. Br J Obstet Gynaecol 92:23.
16. Mandruzzato GP, Bogatti P, Fischer L, Gigli C (1991) The clinical significance of absent or reverse end-diastolic flow in the fetal aorta and umbilical artery. Ultrasound Obstet Gynecol 192-196.
17. Zelop CM, Richardson DK, Heffner LJ (1996) Outcomes of severely abnormal umbilical artery Doppler velocimetry in structurally normal singleton fetuses. Obstet Gynecol 87: 434-438.
18. Wang KG, Chen CP, Yang JM, Su TH (1998) Impact of reverse end-diastolic flow velocity in umbilical artery on pregnancy outcome after 28th gestational week. Acta Obstet Gynecol Scand 77: 527-531.
19. Kurkinen-Raty M, Kivela A, Jouppila P (1997) The clinical significance of an absent end-diastolic velocity in the umbilical artery detected before 34th week of pregnancy. Acta Obstet Gynecol Scand 76: 398-404.
20. Arduini D, Rizzo G, Romanini C (1993) The development of abnormal heart rate patterns after absent end-diastolic velocity in umbilical artery: analysis of risk factors. Am J Obstet Gynecol 168: 43-50.