

COMPARISON OF CEREBRO-PLACENTAL RATIO AND CEREBRO-UTERINE RATIO IN PREDICTING NEONATAL OUTCOME IN PRE ECLAMPTIC PREGNANT WOMEN

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ABSTRACT

AIM: To assess if cerebrouterine ratio would be complementary to cerebroplacental ratio in predicting adverse neonatal outcome in preeclamptic pregnant women

MATERIALS AND METHODS: This research was conducted at the Department of Obstetrics and Gynecology, with clearance from the institute's ethical committee. 100 pre eclamptic pregnant women between 34 to 37 weeks of gestation were included in the study. Cerebroplacental ratio(CP) and cerebrouterine(CU) ratio via latest Doppler USG before delivery was calculated. Patients were followed up till delivery and perinatal outcome was analyzed.

RESULTS: Abnormal CU ratio was seen in 45 cases and CP ratio was seen in 40 cases CU ratio showed statistical significance for preterm births ($p=0.002$), fetal hypoxia (0.02), NICU admission ($p=0.006$). CP ratio showed statistical significance for preterm births ($p<0.001$), low APGAR (0.015), adverse perinatal outcome ($p=0.05$)

Sensitivity for pre term of CU ratio was 71.1% and CP ratio was 72%, for fetal hypoxia sensitivity of CU ratio was 20% and CP ratio was 10%, for low APGAR sensitivity of CU ratio was 77.7% and CP ratio was 77.5%, for low birth weight sensitivity of CU ratio was 60% and CP ratio was 65%, for NICU admission sensitivity of CU ratio was 88.8% and CP ratio was 65% and for adverse perinatal outcome (IUD) sensitivity of CU ratio was 57.7% and CP ratio was 60%.

CONCLUSION: Diagnostic accuracy of CP ratio was almost similar (78%) as compared to CU ratio (75%) in diagnosing the perinatal outcome and was only better than 3%. However, the combined Doppler results were more sensitive to abnormal outcome.

INTRODUCTION

Pre-eclampsia, one of the leading causes of maternal and fetal morbidity and mortality, affecting 2-5% of pregnancies, is a specific syndrome characterized by reduced organ perfusion secondary to vasospasm and endothelial pathophysiology.

Doppler velocimetry of multiple fetoplacental vessels is a noninvasive technique that evaluates abnormal fetal hemodynamics that take place in response to changes in placental resistance, can be used to monitor compromised fetus predicting adverse perinatal outcome and assisting in optimal time of delivery. Doppler of uteroplacental circulation plays a significant role in management of high-risk pregnancies. It helps one to identify the fetus at risk and also helps to time the delivery. Fetal Middle Cerebral Artery (MCA) resistance in combination with Umbilical Artery (UA) resistance as the Cerebroplacental Ratio (CPR) is more reflective of fetal hypoxia and acidemia, and therefore better prediction of perinatal outcome which also aid in the prediction of both SGA and adverse perinatal outcome.

Uterine artery Doppler might be expected to reflect placental perfusion, while umbilical Doppler reflects placental pathology, therefore The Cerebrouterine Ratio (CU Ratio) could have a better predictive value for unfavorable outcome

MATERIALS AND METHODS:

This research was conducted at the Department of Obstetrics and Gynecology, with clearance from the institute's ethical committee. 100 pre eclamptic pregnant women between 34 to 37 weeks of gestation were included in the study. Cerebroplacental ratio(CP) and

cerebrouterine(CU) ratio via latest Doppler USG before delivery was calculated. Patients were followed up till delivery and perinatal outcome was analyzed.

METHODOLOGY:

A well informed written consent was taken. A detailed history was taken for the demographic details, obstetric history, menstrual history, past medical or surgical history. General physical and obstetric examination was done.

Serial scans by transabdominal route were performed if the patient was admitted for safe confinement for interval growth and doppler parameters. The last doppler values before the delivery were considered for this study.

Cerebroplacental ratio and cerebrouterine ratio via latest Doppler USG was calculated at 34-37 weeks for the eligible candidates. Cerebrouterine (CU) ratio was plotted on the chart; <5th percentile was considered as decreased or abnormal.

Cerebroplacental (CP) ratio was considered as abnormal when ratio was <1.08. Patients were followed up till delivery and perinatal outcome was analyzed.

Newborns were assessed based on following factors:

1. Gestational age at birth
2. Birth weight
3. 5 minute APGAR score
4. Mode of delivery
5. NICU admission and the indication if applicable

Women with labor pain, presence of congenital anomalies in the fetus, pregnancies with Rh incompatibility or women with any underlying cardiovascular/metabolic disease were excluded from the study.

Investigations:

Umbilical artery Doppler study

Fetal Middle Cerebral artery Doppler study

Uterine artery doppler study

STATISTICAL ANALYSIS:

Student t test (two tailed, independent) was used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Chi-square/ Fisher Exact test was used to find the significance of study parameters on categorical scale between two or more groups. A statistically significant p-value of 0.005 was used.

Diagnostic accuracy of CP ratio and CU ratio for predicting various neonatal outcomes was calculated by sensitivity, specificity, positive predictive value and negative predictive value using following formulas.

RESULTS:

Table 1: Final outcome of CU and CP ratio

Parameter	CU ratio	CP ratio
Abnormal	45	40
Normal	55	60
Total	100	100

On final outcome, abnormal CU ratio was seen in 45 cases and CP ratio was seen in 40 cases.

Table 2: Comparison between CP and CU ratios in predicting perinatal outcomes

Outcome	CU ratio			CP ratio		
	Abnormal	Normal	P value	Abnormal	Normal	P value
Pre term	32	24	0.002	36	10	<0.0001
Fetal hypoxia	20	03	0.02	19	04	0.5
Low APGAR	30	32	0.1	38	24	0.15
Very low birth weight	28	20	0.2	32	16	0.48
NICU admission	37	17	0.006	35	22	0.07
Perinatal outcome	6	2	0.32	5	3	0.05

CU ratio showed statistical significance for preterm births (p=0.002), fetal hypoxia (0.02), NICU admission (p=0.006).

CP ratio showed statistical significance for preterm births (p<0.001), low APGAR (0.015), adverse perinatal outcome (p=0.05) .

Here Fetal hypoxia was said to exist antenatally, whenever there was absent end diastolic flow or reversal of flow in the umbilical artery, suboptimal NST, and intranatally, when there was thick meconium staining of the amniotic fluid and ominous cardiotocographic changes (persistent and prolonged bradycardia, loss of beat to beat variability, etc.).

Table 3: Overall performance of CU and CP ratios in predicting perinatal outcome

Outcome	CU ratio					CP ratio				
	Sensitivity %	Specificity %	PPV %	NPV %	A %	Sensitivity %	Specificity %	PPV %	NPV %	A %
Pre term	71.1	56.3	57.1	70.4	63	72	60.3	62.8	71.8	64
Fetal hypoxia	20	74.5	39.1 3	53.2	50	10	68.3	17.3	53.2	45
Low APGAR	77.7	32.7	48.6	64.2	53	77.5	31.6	43	67.8	50
Very low birth weight	60	32.7	42.1	50	45	65	36.7	40.6	61.1	48
NICU admission	88.8	40	54.7	81.4	62	65	21.6	35.6	48.1	49
Adverse Perinatal outcome (IUD)	57.7	89.1	57.1	56.9	75	60	90	40	60	78

Sensitivity for pre term of CU ratio was 71.1% and CP ratio was 72%, for fetal hypoxia sensitivity of CU ratio was 20% and CP ratio was 10%, for low APGAR sensitivity of CU ratio was 77.7% and CP ratio was 77.5%, for low birth weight sensitivity of CU ratio was 60% and CP ratio was 65%, for NICU admission sensitivity of CU ratio was 88.8% and CP ratio was 65% and for adverse perinatal outcome (IUD) sensitivity of CU ratio was 57.7% and CP ratio was 60%.

DISCUSSION:

Present study showed that majority 84% were in age group of 21 to 30 years, 10% were <20 years, and only 6% were >30. Study by Mahale N et al ⁽⁵⁾ showed that the mean maternal age was

27.24 years. Nalini YL et al ⁽⁸⁾ in their study showed that majority were in age group of 21 to 25 years. Present study showed that 60% were primipara and 40% were multipara. Study by Mahale N et al ⁽⁵⁾ showed that the majority 66% were primipara and 34% were multipara. Present study showed similar results. Average period of gestation was 35.34 ± 1.2 weeks. Range being 34 to 37 weeks. 85% were in range of 34 to 36 weeks, and only 15% were more than 36 weeks. Average period of gestation was 35.34 ± 1.2 weeks. On final outcome, abnormal CU ratio was seen in 45 cases and CP ratio was seen in 40 cases. Study by Adiga et al ⁽⁸¹⁾ showed that CU ratio was better in predicting adverse event than CP ratio. 24% had a vaginal delivery and 76% underwent LSCS.

Neonatal parameters :

On APGAR score, where 62% had ≤ 7 and 38% had > 7 score. 57% were admitted in NICU and 43% did not need admission. Study by Mahale N et al ⁽⁵⁾ showed that 76% of the newborn were admitted to NICU and 24% were normal. Similar findings were seen in present study. Nalini YL et al ⁽⁸⁾ in their study showed that 40% of newborn had NICU admission. Study by Rekha BR et al ⁽⁷⁹⁾ showed that 77.8% were admitted to NICU. Study by Adiga et al ⁽⁸¹⁾ showed that 50.5% babies required NICU admission. 64% had no complication, 20% had hyperbilirubinemia, and 18% had fetal hypoxia, 12% had acidemia and 2% polycythemia. Study by Mahale N et al showed that ⁽⁵⁾ 36% had hyperbilirubinemia followed by hypoglycemia in 12%, 4% had hypothermia and 4% had thrombocytopenia. Similar findings were seen in present study. Study by Adiga et al ⁽⁸¹⁾ showed that 10.5% had acidemia, 34.7% had hyperbilirubinemia, 1.05% had neonatal seizures.

In the present study, 92% birth were alive and only 8% had an IUD. Study by Mahale N et al showed that ⁽⁵⁾ the on perinatal outcome 14% died and 86% were alive and discharged in good health. Study by Adiga et al ⁽⁸¹⁾ showed that 5.2% had IUD.

48% had weight < 2 kg, 40% had > 2 kg, to 3 kg and 12% had > 3 kg. Average birth weight was 1779.96 ± 512.2 . Study by Mahale N et al ⁽⁵⁾ showed that maximum of babies had birth weight between 1 to 15 kg at birth. 2 babies weighed less than 1 kg. Nalini YL et al ⁽⁸⁾ in their study showed that 4% had low birth weight. Study by Rekha BR et al ⁽⁷⁹⁾ showed that majority 91.7% were having birth weight in range of 1.5 to 2.5 kg. Study by Gyawali M et al ⁽⁸⁰⁾ showed that mean birth weight was 2.1 kg with a range of 1.45 kg to 3.75 kg. Similar findings were seen in present study. Majority of newborn were alive and only 12.06% died.

In the present study CU ratio showed statistical significance for preterm births ($p=0.002$), fetal hypoxia (0.02), NICU admission ($p=0.006$). CP ratio showed statistical significance for preterm births ($p<0.001$), low APGAR (0.015), adverse perinatal outcome ($p=0.05$).

Study by Adiga et al ⁽⁸¹⁾ showed similar results. Their study showed significance for preterm, acidemia, fetal hypoxia, low APGAR and perinatal outcome for CU ratio and for CP ratio in preterm, acidemia, low APGAR, HMD and perinatal outcome. Simanaviciute and Gudmundsson found significant correlation with SGA newborn independently with abnormal CP ratio and found no significance for low APGAR ¹⁰⁰.

In present study Sensitivity for pre term of CU ratio was 71.1% and CP ratio was 72%, for fetal hypoxia sensitivity of CU ratio was 20% and CP ratio was 10%, for low APGAR sensitivity of CU ratio was 77.7% and CP ratio was 77.5%, for low birth weight sensitivity of CU ratio was 60% and CP ratio was 65%, for NICU admission sensitivity of CU ratio was 88.8% and CP ratio was 65% and for adverse perinatal outcome (IUD) sensitivity of CU ratio was 57.7% and CP ratio was 60%.

Study by Adiga et al ⁽⁸¹⁾ showed that Sensitivity for pre term of CU ratio was 54.5% and CP ratio was 33.3%, low APGAR of CU ratio was 62.5% and CP ratio was 56.3%

Diagnostic accuracy of CP ratio is good (78%) as compared to CU ratio (75%) in diagnosing the perinatal outcome.

Study by Adiga et al ⁽⁸¹⁾ showed that CP ratio gives good diagnosis as compared to CU ratio.

CONCLUSION:

Diagnostic accuracy of CP ratio was almost similar (78%) as compared to CU ratio (75%) in diagnosing the perinatal outcome and was only better than 3%. However, the combined Doppler results were more sensitive to abnormal outcome.

REFERENCES:

1. Jaideep KC PD, Girija A. Prevalence of high risk among pregnant women attending antenatal clinic in rural field practice area of Jawaharlal Nehru Medical College, Belgavi, Karnataka, India. 2017. 2017;4(4):3.
2. Scott KE, Usher R. Fetal malnutrition: its incidence, causes, and effects. *American Journal of Obstetrics & Gynecology*. 1966;94(7):951-63.
3. Peleg D, Kennedy CM, Hunter SK. Intrauterine growth restriction: identification and management. *Am Fam Physician*. 1998;58(2):453-60, 66-7.
4. Frøen JF, Gardosi JO, Thurmann A, Francis A, Stray-Pedersen B. Restricted fetal growth in sudden intrauterine unexplained death. *Acta obstetrica et gynecologica Scandinavica*. 2004;83(9):801-7.
5. De Bono M, Fawdry RD, Lilford RJ. Size of trials for evaluation of antenatal tests of fetal wellbeing in high risk pregnancy. *J Perinat Med*. 1990;18(2):77-87.
6. Trudinger BJ, Cook CM, Thompson RS, Giles WB, Connelly A. Low-dose aspirin therapy improves fetal weight in umbilical placental insufficiency. *Am J Obstet Gynecol*. 1988;159(3):681-5.
7. Hoffman C, Galan HL. Assessing the 'at-risk' fetus: Doppler ultrasound. *Curr Opin Obstet Gynecol*. 2009;21(2):161-6.
8. Symonds EM. Antenatal, perinatal, or postnatal brain damage? *Br Med J (Clin Res Ed)*. 1987;294(6579):1046-7.
9. Khanduri S, Chhabra S, Yadav S, Sabharwal T, Chaudhary M, Usmani T, et al. Role of Color Doppler Flowmetry in Prediction of Intrauterine Growth Retardation in High-Risk Pregnancy. *Cureus*. 2017;9(11):e1827.
10. Cruz-Martinez R, Figueras F. The role of Doppler and placental screening. *Best Pract Res Clin Obstet Gynaecol*. 2009;23(6):845-55.
11. Trudinger BJ, Cook CM, Giles WB, Connelly A, Thompson RS. Umbilical artery flow velocity waveforms in high-risk pregnancy. Randomised controlled trial. *Lancet*. 1987;1(8526):188-90.
12. McParland P, Pearce JM, Chamberlain GV. Doppler ultrasound and aspirin in recognition and prevention of pregnancy-induced hypertension. *Lancet*. 1990;335(8705):1552-5.
13. Al Qahtani N. Doppler ultrasound in the assessment of suspected intra-uterine growth restriction. *Ann Afr Med*. 2011;10(4):266-71.
14. Arduini D., Rizzo G. Prediction of fetal outcome in small for gestational age fetuses: comparison of Doppler measurements obtained from different fetal vessels. *Journal of Perinatal Medicine*. 1992;20(1):29-38.
15. Harrington K., Thompson M. O., Carpenter R. G., Nguyen M., Campbell S. Doppler fetal circulation in pregnancies complicated by pre-eclampsia or delivery of a small for gestational age baby: 2. Longitudinal analysis. *BJOG: An International Journal of Obstetrics & Gynaecology*. 1999;106(5):453-466.
16. Simanaviciute D., Gudmundsson S. Fetal middle cerebral to uterine artery pulsatility index ratios in normal and pre-eclamptic pregnancies. *Ultrasound in Obstetrics and Gynecology*. 2006;28(6):794-801.
17. Mohan S, Natarajan P, Madineni S, Rajasekhar K. Study of Triple Vessel Wave Pattern by Doppler Studies in Low Risk and High Risk Pregnancies and Perinatal Outcome. *IOSR Journal of Dental and Medical Sciences*. 2017; 16: 14-23. <https://goo.gl/DVfrQw>

18. Smitha K, Sowmya K, Malathi T. Study of Doppler waveforms in pregnancy induced hypertension and its correlation with perinatal outcome. IJRCOG. 2014; 3: 428-433. <https://goo.gl/5PFKgp>
19. Tushar Patil, Amit C. Shah. "Doppler Analysis in Pregnancy Induced Hypertension". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 71, December 18; Page: 15120-15147
20. Vikram Patil, Sahana Gowda, Sudha DAS, KB Suma, Rudresh Hiremath, Sachin Shetty, Vinay Raj, MR Shashikumar. Cerebro-Placental Ratio in Women with Hypertensive Disorders of Pregnancy: A Reliable Predictor of Neonatal Outcome. Journal of Clinical and Diagnostic Research. 2019 May, Vol-13(5): TC06-TC10
21. Sarosh Rana, Elizabeth Lemoine, Joey P. Granger and S. Ananth Karumanchi. Preeclampsia Pathophysiology, Challenges, and Perspectives. Circulation Research. 2019;124:1094–1112.
22. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013; 122:1122–1131.
23. Palei AC, Spradley FT, Warrington JP, George EM, Granger JP. Pathophysiology of hypertension in pre-eclampsia: a lesson in integrative physiology. Acta Physiol (Oxf). 2013; 208:224–233.
24. Ligia Maria Suppo de Souza Rugolo, Maria Regina Bentlin, MD; Cleide Enoir Petean Trindade. Preeclampsia: Early and Late Neonatal Outcomes. Neoreviews (2012) 13 (9): e532–e541.
25. Katarzyna A. Stefanska¹, Maciej Zielinski², Joanna Jassem-Bobowicz³, Dorota Zamkowska. Perinatal and neonatal outcome in patients with preeclampsia. Ginekol Pol 2022;93(3):203-208.
26. Al Qahtani N. Doppler ultrasound in the assessment of suspected intra-uterine growth restriction. Ann Afr Med. 2011;10(4):266-71.
27. Stuart Campbell. The prediction of fetal maturity by ultrasonic measurement of the biparietal diameter. J. Obstet. Gynaec. Brit. Cwith July 1969; 76: 603-609.
28. Rumack CM, Wilson SR, Charboneau JW. Diagnostic Ultrasound 3rd ed. Elsevier Mosby, 2005.
29. Hausmann M, Hackloer BJ, Standach A. Ultrasound Diagnosis in Obstetrics and Gynecology. Springer-Verlag, Berlin, Germany. 1986; 1:23.
30. Kurts AB, Wapner RJ, Kurtz RJ et al. Analysis of biparietal diameter as an accurate indicator of gestational age. J Clin Ultrasound 1980; 8:319-326.
31. Di Renzo GC, Luzi G, Clerici G, Carrera JM. Antenatal diagnosis of intrauterine growth retardation. In: Kurjak A (Ed.). Textbook of Perinatal Medicine. The Parthnon Publish, London 1998; 1201-11.
32. Law RG, MacRae KD. Head circumference as an index of fetal age. J Ultrasound Med 1982; 1:281-288.
33. Hadlock FP, Deter RL, Harrist RB et al. Fetal abdominal circumference as a predictor of menstrual age. Am J Radiol 1982; 152:497-501.
34. Honarvar M, Allahyari M, Dehbashi S. Assessment of gestational age based on ultrasonic femur length after the first trimester: A simple mathematical correlation between gestational age and femur length. Int J Gynecol Obstet 2000; 70:335-340.
35. Hadlock FP, Deter RL, Harrist RB et al. Computer-assisted analysis of fetal age in the third trimester using multiple fetal growth parameters. J Clin Ultrasound 1983; 11:313-316.
36. Phelan JP, Ahn MO, Smith CV et al. Amniotic fluid index measurements during pregnancy. J Reprod Med 1987; 32:601-604.
37. Hagen-Ansert SL. Textbook of Diagnostic Ultrasonography 5th ed. 2001; Mosby, USA.
38. Manning FA, Platt LD, Sipos L. Antepartum fetal evaluation: Development of fetal biophysical profile score. Am J Obstet Gynecol 1980; 136:787-795.

39. Manning FA, Morrison I, Lange IR et al. Fetal biophysical profile scoring: A prospective study in 1184 high-risk patients. *Am J ObstetGynecol* 1981; 140:289-294.
40. Dutta DC. *Textbook of Obstetrics*. New Central Book agency. 5th ed. 2005.
41. National Institute of Child Health and Human Development Research Planning Workshop. Electronic fetal heart rate monitoring: Research guidelines for interpretation. *Am J ObstetGynecol* 1987; 156:527.
42. Baschat AA. Pathophysiology of fetal growth restriction: Implications for diagnosis and surveillance. *ObstetGynecolSurv* 2004; 59(8):617.
43. Romero R, Kalache KD, Kadar N. Timing the delivery of the preterm severely growth-restricted fetus: venous Doppler, cardiotocography on the biophysical profile? *Opinion in Ultrasound ObstetGynecol* 2002; 19:118.
44. Brosens I, Robertson WB, Dixon HG. The physiological response of the vessels of the placental bed to normal pregnancy. *J PatholBacteriol* 1967;93:569-79.
45. Sheppard BL, Bonnar J. An ultrastructural study of utero-placental spiral arteries in hypertensive and normotensive pregnancy and fetal growth retardation. *Br J ObstetGynaecol* 1981;88:695-705.
46. Scherjon SA, Smolders-DeHaas H, Kok JH, Zondervan HA. The "brain-sparing" effect: antenatal cerebral Doppler findings in relation to neurologic outcome in very preterm infants. *Am J Obstet Gynecol*. 1993 Jul;169(1):169-75.
47. Baschat AA, Gembruch U, Reiss I et al. Relationship between arterial and venous Doppler and perinatal outcome in fetal growth restriction. *Ultrasound ObstetGynecol* 2000; 16:417-413.
48. Giles WB, Trudinger BJ, Baird PJ. Fetal umbilical artery flow velocity waveforms and placental resistane: pathological correlation. *Br J ObstetGynaecol* 1985; 92:31.
49. Wladimiroff JW, vanWijngaard JAGW, Degani S, Noordam MJ, van Eijck J, Tonge HM. Cerebral and umbilical arterial blood flow velocity waveforms in normal and growth retarded pregnancies. *ObstetGynecol* 1987; 69:705-9.
50. Wladimiroff JW, Tonge HM, Stewart PA. Doppler ultrasound assessment of cerebral blood flow in the human fetus. *Br J ObstetGynaecol* 1986; 93:471.
51. Kiserud T, Eik-Nes SH, Blaas HG, Hellevik LR, Simensen B. Ductus venosus blood velocity and the umbilical circulation in the seriously growth-retarded fetus. *Ultrasound ObstetGynecol* 1994; 4: 109-14.
52. Hecher K, Snijders R, Campbell S, Nicolaidis KH. Fetal venous, intracardiac, and arterial blood flow measurements in intrauterine growth retardation: relationship with fetal blood gases. *Am J ObstetGynecol* 1995; 173:10-15.
53. Maulik D (Ed.). *Doppler Ultrasound in Obstetrics and Gynecology* 2nd ed. 2005; Springer-Verlag, Berlin, Germany.
54. Takahashi Y, Kawabata I, Tamaya T. Characterization of growth-restricted fetuses with breakdown of the brain-sparing effect diagnosed by spectral Doppler. *J Matern Fetal Med* 2001 Apr; 10(2):122-6.
55. Fleischer AC, Manning FA, Jeanty P, Romero R. *Sonography in Obstetrics and Gynecology – Principles and Practice* 5th ed. 1996; Appleton-Lange.
56. Boyd JD, Hamilton WJ. *The Human Placenta*. Cambridge: Heffer& Sons, 1970:207-74.
57. Ramsey EM, Corner GW, Donner MW. Serial and cineradioangiographic visualization of maternal circulation in the primate (hemochorial) placenta. *Am J ObstetGynecol* 1963; 86:213-25.
58. Brosens I, Robertson WB, Dixon HG. The physiological response of the vessels of the placental bed to normal pregnancy. *J PatholBacteriol* 1967, 93:569-79
59. Pijnenborg R, Bland JM, Robertson WB, Brosens I. Uteroplacental arterial changes related to interstitial trophoblast migration in early human pregnancy. *Placenta* 1983; 4:387-414

60. Khong TY, De Wolf F, Robertson WB et al: Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational age infants. *Br J ObstetGynaecol* 1986; 93:1049-1059
61. FiltzGeraldDE, Drumm J. Noninvasive measurement of human fetal circulation using ultrasound: A new method. *Br Med J* 1977; ii:1450-51.
62. Stuart B, Drumm JE, FitzGeraldDE, DuignanNM. Fetal blood flow velocity waveforms in normal pregnancy *Br J ObstetGynaecol* 1980; 87:780-786.
63. Kaufmann P, Luckhardt M, Leiser R. Three dimensional representation of the fetal vessel system in the human placenta. *Trophoblast Res* 1984; 3:113-138.
64. Mari G, Moise KJ Jr, Deter RL et al. Doppler assessment of the pulsatility index in the cerebral circulation of the human fetus. *Am J ObstetGynecol* 1989; 160:698-703.
65. Woo JK, Liang ST, Lo RS, Chan FY. Middle cerebral artery Doppler flow velocity waveforms *ObstetGynecol* 1987; 70:613-616.
66. Bilardo CM, Campbell S, Nicolaidis KH. Mean blood velocities and flow impedance in the fetal descending thoracic aortic and common carotid artery in normal pregnancy. *Early Hum Dev* 1988; 18:213-21.
67. Soregaroli M, Bonera R, Danti L, Dinolfo D, Taddei F, Valcamonico A, Frusca T. Prognostic role of umbilical artery Doppler velocimetry in growth-restricted fetuses. *J Matern Fetal Neonatal Med* 2002; 11(3):199-203.
68. Seyam YS, Al-Mahmeid MS, Al-Tamimi HK. Umbilical artery Doppler flow velocimetry in intrauterine growth restriction and its relation to perinatal outcome. *Int J GynaecolObstet* 2002 May; 77(2):131-7.
69. Figueras F, Eixarch E, Gratacos E, Gardosi J. Predictiveness of antenatal umbilical artery Doppler for adverse pregnancy outcome in small-for-gestational-age babies according to customised birthweight centiles: population-based study. *BJOG* 2008 Apr; 115(5):590-4.
70. Malhotra N, Chanana C, Kumar S, Roy K, Sharma JB. Comparison of perinatal outcome of growth-restricted fetuses with normal and abnormal umbilical artery Doppler waveforms. *Indian J Med Sci* 2006 Aug; 60(8):311-7.
71. McCowan LM, Harding JE, Stewart AW. Umbilical artery Doppler studies in small for gestational age babies reflect disease severity. *BJOG* 2000 Jul; 107(7):916-25.
72. Baschat AA, Gembruch U, Reiss I, Gortner L, Weiner CP, Harman CR. Absent umbilical artery end-diastolic velocity in growth-restricted fetuses: a risk factor for neonatal thrombocytopenia. *ObstetGynecol* 2000 Aug; 96(2):162-6.
73. BhattAB, Tank PD, Barmade KB, Damania KR. Abnormal Doppler flow velocimetry in the growth restricted foetus as a predictor for necrotising enterocolitis. *J Postgrad Med* 2002 Jul-Sep; 48(3):182-5; discussion 185.
74. Szymański M, Szymański W, Semeńczuk M, Skublicki S. Relationship between Doppler velocimetry at middle cerebral artery and umbilical artery and status of newborn after delivery. *Ginekol Pol* 2005 Sep; 76(9):713-9.
75. Yildirim G, Turhan E, Aslan H, Gungorduk K, Guven H, Idem O, Ceylan Y, Gulkilik A. Perinatal and neonatal outcomes of growth restricted fetuses with positive end diastolic and absent or reversed umbilical artery doppler waveforms. *Saudi Med J* 2008 Mar; 29(3):403-8.
76. Shand AW, Hornbuckle J, Nathan E, Dickinson JE, French NP. Small for gestational age preterm infants and relationship of abnormal umbilical artery Doppler blood flow to perinatal mortality and neurodevelopmental outcomes. *Aust N Z J ObstetGynaecol* 2009; 49(1):52-8.
77. Spinillo A, Montanari L, Roccio M, Zanchi S, Tziella C, Stronati M. Prognostic significance of the interaction between abnormal umbilical and middle cerebral artery Doppler velocimetry in pregnancies complicated by fetal growth restriction. *ActaObstetGynecolScand* 2009; 88(2):159-66.
78. Wienerroither H, Steiner H, Tomaselli J, et al. Intrauterine blood flow and long-term intellectual, neurologic, and social development. *ObstetGynecol* 2001 Mar; 97(3):449-53.

79. Gerber S, Hohlfeld P, Viquerat F, Tolsa JF, Vial Y. Intrauterine growth restriction and absent or reverse end-diastolic blood flow in umbilical artery (Doppler class II or III): A retrospective study of short- and long-term fetal morbidity and mortality. *Eur J ObstetGynecolReprodBiol* 2006 May 1; 126(1):20-6.
80. Hershkovitz R, Kingdom JC, Geary M, Rodeck CH. Fetal cerebral blood flow redistribution in late gestation: identification of compromise in small fetuses with normal umbilical artery Doppler. *Ultrasound ObstetGynecol* 2000 Mar; 15(3):209-12.
81. Sarkar P, Johnson P, Stojilkovic. Middle cerebral artery Doppler in severe intrauterine growth restriction. *Ultrasound ObstetGynecol* 2001 May; 17(5):416-20.
82. Piazzze J, Padula F, Cerekja A, Cosmi EV, Anceschi MM. Prognostic value of umbilical-middle cerebral artery pulsatility index ratio in fetuses with growth restriction. *Int J GynaecolObstet* 2005 Dec; 91(3):233-7.
83. Vergani P, Roncaglia N, Locatelli A, Andreotti C, Crippa I, Pezzullo JC, Ghidini A. Antenatal predictors of neonatal outcome in fetal growth restriction with absent end-diastolic flow in the umbilical artery. *Am J ObstetGynecol* 2005 Sep; 193(3 Pt 2):1213-8.
84. Odibo AO, Riddick C, Pare E, Stamilio DM, MaconesGA. Cerebro-placental Doppler ratio and adverse perinatal outcomes in intrauterine growth restriction: evaluating the impact of using gestational age-specific reference values. *J Ultrasound Med* 2005 Sep; 24(9):1223-8.
85. Alataş C, Aksoy E, Akarsu C, Yakin K, Bahçeci M. Prediction of perinatal outcome by middle cerebral artery Doppler velocimetry. *Arch GynecolObstet* 1996; 258(3):141-6.
86. Strigini FA, De Luca G, Lencioni G, Scida P, Giusti G, Genazzani AR. Middle cerebral artery velocimetry: different clinical relevance depending on umbilical velocimetry. *ObstetGynecol* 1997 Dec; 90(6):953-7.
87. Romero Gutiérrez G, Ramírez Hernández GL, Molina Rodríguez R, Ponce de León AL, Cortés Salim P Predictive value of Doppler fluxometry of umbilical and middle cerebral arteries with the perinatal outcomes in fetus with intrauterine growth restriction. *GinecolObstet Mex* 2009 Jan; 77(1):19-25.
88. Dubiel M, Gudmundsson S, Gunnarsson G, Marsál K. Middle cerebral artery velocimetry as a predictor of hypoxemia in fetuses with increased resistance to blood flow in the umbilical artery. *Early Hum Dev* 1997 Jan 20; 47(2):177-84.
89. Madazli R, Uludağ S, Ocak V. Doppler assessment of umbilical artery, thoracic aorta and middle cerebral artery in the management of pregnancies with growth restriction. *ActaObstetGynecolScand* 2001 Aug; 80(8):702-7.
90. Fong KW, Ohlsson A, Hannah ME, Grisaru S, Kingdom J, Cohen H, Ryan M, Windrim R, Foster G, Amankwah K. Prediction of perinatal outcome in fetuses suspected to have intrauterine growth restriction: Doppler US study of fetal cerebral, renal, and umbilical arteries. *Radiology*. 1999 Dec; 213(3):681-9.
91. Rekha BR, Pavanaganga A, Lakshmi SMPA, Nagarathnamma R. Comparison of Doppler findings and neonatal outcome in fetal growth restriction. *Int J ReprodContraceptObstetGynecol* 2017;6:955-8.
92. Aparna G SV. A study of colour doppler in high risk pregnancies. *International Journal of Contemporary Medical Research* 2018;5(4):D13-D17.
93. Tabitha S, Rajini M. The study of arterial and venous Doppler in high risk pregnancies and its role in perinatal outcome. 2018. 2018;7(3):7.
94. Dubiel M, Breborowicz GH, Marsal K, Gudmundsson S. Fetal adrenal and middle cerebral artery Doppler velocimetry in high-risk pregnancy. *Ultrasound Obstet Gynecol*. 2000;16(5):414-8.
95. Banu AA. Doppler velocimetry in the umbilical and middle cerebral arteries in fetuses with intrauterine growth retardation or fetal distress. *Fukuoka Igaku Zasshi*. 1998;89(5):133-44.
96. Cheema R, Dubiel M, Breborowicz G, Gudmundsson S. Fetal cerebral venous Doppler velocimetry in normal and high-risk pregnancy. *Ultrasound Obstet Gynecol*. 2004;24(2):147-53.

97. El Guindy AE, Nawara M, ElSanter O. Cerebroplacental Ratio and Cerebrouterine Ratio in Predicting Neonatal Outcome in Preeclamptic Pregnant Women. *Int J Reprod Med Gynecol.* 2018;4(1): 022-027.
98. Karge, A.; Lobmaier, S.M.; Haller, B.; Kuschel, B.; Ortiz, J.U. Value of Cerebroplacental Ratio and Uterine Artery Doppler as Predictors of Adverse Perinatal Outcome in Very Small for Gestational Age at Term Fetuses. *J. Clin. Med.* 2022, 11, 3852.
99. Adiga P, Kantharaja I, Hebbar S, Rai L, Guruvare S, Mundkur A. Predictive Value of Middle Cerebral Artery to Uterine Artery Pulsatility Index Ratio in Hypertensive Disorders of Pregnancy. *International Journal of Reproductive Medicine.* 2015.
100. D. Simanaviciute and S. Gudmundsson, "Fetal middle cerebral to uterine artery pulsatility index ratios in normal and preeclamptic pregnancies," *Ultrasound in Obstetrics and Gynecology*, vol. 28, no. 6, pp. 794–801, 2006.