Fetal Cerebral to Umbilical Ratio in Proteinuric Hypertensive Pregnancies

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SUMMARY

Objective: The aim of this study was to evaluate the ratio of the middle cerebral artery pulsatility index (MCA PI) to umbilical artery pulsatility index (UA PI) in proteinuric hypertensive pregnancies and to compare its reliability with a control group.

Material and Methods: We evaluated 81 pregnant women representing clinical forms of preeclampsia or eclampsia at the third trimester of pregnancy. Seventy-three cases with no sign of preeclampsia or eclampsia were accepted as controls. Clinical and laboratory characteristics were recorded. Pulse wave color Doppler with 3.5MHz probe was used in the assessments of fetal and maternal circulation. Cerebral to umbilical ratio was obtained by the division of MCA PI to UA PI.

Results: Uterine artery notching, absent end diastolic flow in fetal arteries, intrauterine growth restriction, cesarean section, neonatal morbidity and perinatal mortality were found statistically higher in the study group than controls. Cerebral to umbilical ratio of the hypertensive group was 1.20±0.53, and was 1.74±0.53 of the control one ($p<0.001$). Sensitivity, specificity and predictive values of complications were found higher in the combined test than single tests.

Conclusions: Lower values observed at cerebral to umbilical ratio (<1.2) were significantly associated with complications of proteinuric hypertension at the third trimester of the pregnancy. The cerebral to umbilical ratio may be more useful than umbilical and cerebral evaluations alone in the prediction of these complications.

Key Words: Proteinuric hypertensive pregnancy, Middle cerebral artery pulsatility index, Umbilical artery pulsatility index, Cerebral to umbilical ratio

ÖZET

PROTEİNÜRİK HİPERTANSİF GEBELİKLERDE FETAL SEREBRAL - UMBİLİKAL ORAN

Amaç: Bu çalışmanın amacı proteinürik hipertansif gebeliklerde orta serebral arter pulsatilite indeksi (OSA PI) / umbilikal arter pulsatilite indeksi (UA PI) oranını değerlendirmek ve bu oranın güvenilirliğini kontrol grubu ile karşılaştırmaktır.

Yöntem: Gebeliğin üçüncü trimesterinde preeklampsi veya eklampsi tanısı ile izlenen 81 gebe ile, kontrol grubunu oluşturan 73 normal gebe klinik ve laboratuvar özellikler yönünden değerlendirmeye alındı. Fetal ve maternal dolaşımların Doppler değerlendirmesinde 3.5MHz dupleks prob kullanıldı. Serebral-umbilikal oran OSA PI değerinin UA PI değerine bölünmesi ile elde edildi.

Bulgular: Uterin arterlerde çentiklenme, fetal arterlerde diyastol sonu akım yokluğu, intrauterin gelişme kısıtlılığı, sezaryen, neonatal morbidite ve perinatal mortalite hipertansif grupta kontrol grubuna göre istatistiksel olarak daha yüksek bulundu. Serebral-umbilikal oran hipertansif grupta 1.20±0.53, kontrol grubunda ise 1.74±0.53 idi. Komplikasyonların saptanmasında duyarlılık, belirginlik ve tahmin serebral-umbilikal oran kullanıldığında daha yüksek bulundu.

Sonuç: Gebeliğin 3. trimesterinde serebral-umbilikal oranda gözlenen düşük değerler (<1.2) proteinürik hipertansiyonun komplikasyonları ile anlamlı oranda birlikte bulunmaktadır. Bu komplikasyonların önceden tahmininde, serebral-umbilikal oranın kullanımı, serebral veya umbilikal ölçümlerin tek tek kullanılmasına göre daha yararlı olabilir.

Anahtar Kelimeler: Proteinürik hipertansif gebelik, Orta serebral arter pulsatilite indeksi, Umbilikal arter pulsatilite indeksi, Serebral-umbilikal oran

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Hypertension is one of the most frequent (5-10%) and most important event in pregnancy. It is associated with high perinatal morbidity and mortality. Techniques to understand and predict this entity are a subject for many studies in obstetrics (1).

Conventional fetal well being tests such as measurement of fetal growth by ultrasound, nonstress or contraction stress tests and biophysical profile are used to assess high risk pregnancies. Recently umbilical artery (UA) Doppler studies are widely used for the prediction of fetal compromise (2).

Evaluation of the cerebral circulation can grant some useful information on this subject (3-6). Because of the discrepancies between Doppler findings of umbilical and middle cerebral artery (MCA) in some circumstances (7-9), detailed Doppler assessments like middle cerebral to umbilical artery ratio (MCA/UA) are proposed for better evaluation (10-12).

The aim of this study was to compare the values of the umbilical artery and middle cerebral artery pulsatility indices (PI) and the ratio of these indices in proteinuric hypertensive and normal pregnancies, and to evaluate the most accurate diagnostic Doppler index showing concordance with clinical and laboratory findings.

METHODS

A total number of 154 singleton pregnancies ranging between 27 and 41 gestational weeks and without fetal abnormality were evaluated in a cross-sectional study at Dicle University Medical Faculty between 1994-1997 years. Seventy-three uncomplicated pregnancies with a term delivery were used to define the normal group. The study population comprised 81 hypertensive proteinuric pregnant women. Demographic findings such as age, gravidity and parity, clinical findings such as gestational age (weeks of amenorrhoae), hypertension (persistent systolic blood pressure above 140mmHg or diastolic blood pressure above 90mmHg), mode of delivery (vaginal or abdominal), intrauterine growth restriction (IUGR) (birth weight below 10th percentile), low Apgar scores (5th minute: <7), prenatal or early neonatal mortality and morbidity (neonatal intensive care unit for more than 12 hours), laboratory findings such as proteinuria (+ or more, at least two times daily), creatinine, uric acid, hematocrite, hemoglobine levels were all recorded. Twenty-six cases had received antihypertensive treatment (nifedipine ± methyldopa), 5 cases anticonvulsive treatment (magnesium sulfate) and 21 cases both before the Doppler examination in the proteinuric hypertensive group. No medication was done to the control group. Clinical management was not influenced especially by Doppler results.

The cases were evaluated with duplex Doppler ultrasonography (TOSHIBA SSA-270 and SSH-140A, 3.75 MHz curvilinear transducer). Signals were recorded from the distal part or the proximal ascending branch of the uterine artery by placing the Doppler transducer to 2 to 3 cm medial to the anterior superior iliac spine, a free loop of the umbilical artery, fetal descendent aorta and lateral branch of the circle of Willis at the base of the skull. Notching on uterine arteries was assessed according the description of Schulman et al (13). At least 5 uniform waveforms were observed in fetal rest position. Two of them were traced and the mean value for PI was calculated.

Doppler results such as notching on uterine artery, absent end diastole (AED) in umbilical artery and aorta, averages of UA PI, MCA PI, MCA/UA, laboratory values, incidences of prematurity, IUGR, low Apgar score at the 5th minute, cesarean section rate, neonatal morbidity and perinatal mortality were compared on both group. In the comparison of standard diagnostic tests in hypertensive cases, we used the cutoff value calculated by 1 standard deviation (SD) below (for MCA PI: 1.27; for MCA PI /UA PI: 1.21) or above (for UA PI: 1.24) the mean of the control group. Statistical analysis was performed with the Student's t test for unpaired observations, by Pearson's correlation in relationship and by X2 or Fisher's exact test for the differences in the incidence. Statistical significance was defined as a probability value of <0.05.

RESULTS

Clinical, laboratory and demographic findings of 81 proteinuric hypertensive pregnant and of 73 control are shown at the Table 1. Hematocrite and hemoglobine levels were slightly higher in the hypertensive pregnant group than control one. Renal function of the study group showed pathologic features also. Sonographic gestational age and Doppler findings of the groups are shown at the Table 2. Pathologic Doppler findings on uteroplacental and fetal arteries were seen frequently in the proteinuric hypertensive pregnant women. In the study group, both MCA and UA PI averages differed from those of the control. The average of MCA PI was lower, of UA PI was higher in the study group than control group. MCA/UA was low in the study group (Figure 1,2).

The average of the time interval from Doppler investigation to delivery was 4.96±12.32 days in the study group and was 29.56±28.87 days in the control one ($p<0.001$). Delivery characteristics, neonatal findings and outcomes of the groups are

Table 1. Clinical, Laboratory and Demographic Findings of Hypertensive Proteinuric and Control Groups (Mean±SD)

	Hypertensive Group (n = 81)	Control Group (n = 73)	p
Age	28.83 ± 6.45	27.15 ± 4.32	NS
Gravida	4.30 ± 3.36	3.45 ± 2.24	NS
Para	3.31 ± 2.14	2.60 ± 1.90	NS
Sistolic BP (mmHg)	153.67 ± 19.02	111.40 ± 9.22	< 0.001
Diastolic BP (mmHg)	96.89 ± 12.25	70.01 ± 8.45	< 0.001
Hematocrite (%)	35.70 ± 5.11	34.34 ± 3.13	< 0.05
Hemoglobine (g/dl)	12.19 ± 2.34	11.39 ± 2.17	< 0.05
Urea (mg/dl)	24.82 ± 14.54	18.90 ± 7.68	< 0.01
Creatinine (mg/dl)	0.98 ± 0.68	0.65 ± 0.18	< 0.001
Uric acid (mg/dl)	6.12 ± 2.39	4.23 ± 0.94	< 0.001

NS : Not Significant
BP: Blood pressure

Table 2. Sonographic Gestational Age and Doppler Findings of Hypertensive Proteinuric Pregnant Women and Controls (Mean±SD)

	Hypertensive Group (n = 81)	Control Group (n = 73)	p
Gestational week	34.29 ± 3.64	34.61 ± 4.14	NS
MCA PI	1.37 ± 0.43	1.69 ± 0.42	< 0.001
UA PI	1.20 ± 0.40	1.03 ± 0.21	< 0.001
MCA/UA	1.20 ± 0.53	1.74 ± 0.53	< 0.001
Uterine artery notching (n)	43	14	< 0.001
Aortic AED (n)	9	0	< 0.01
Umbilical artery AED (n)	7	0	< 0.05

NS : Not Significant
MCA : Middle Cerebral Artery
PI : Pulsatility Index
UA : Umbilical Artery
MCA/UA : Middle Cerebral Artery PI / Umbilical Artery PI Ratio
AED : Absent End Diastole

shown on the Table 3. Birth weights, 5th minute Apgar scores, IUGR, prematurity, cesarean section rate, neonatal morbidity and perinatal mortality were high in the hypertensive proteinuric group. Intrauterine fetal demise was observed in three cases in the study group but none in the control group. In the perinatal mortality group (n:8), abnormal UA PI was found in 87%, abnormal MCA PI in 37% and abnormal MCA /UA in 75% of the cases while their mean of MCA /UA was 0.95 ±0.23.

In the prediction of clinical complications in proteinuric hypertension, cerebral-umbilical ratio (<1.2) showed the best results when compared with UA PI or MCA PI alone (Table 4).

Table 3. Delivery Characteristics, Neonatal Findings and Perinatal Outcomes of Hypertensive Proteinuric Pregnant Women and Controls (Mean±SD)

	Hypertensive Group (n = 81)	Control Group (n = 73)	p
Birth weight (g)	2407 ± 902	3468 ± 382	< 0.001
Apgar 5th minute	7.38 ± 2.64	9.41 ± 0.85	< 0.001
Apgar 5th minute <7 (n)	25	2	< 0.001
IUGR (n)	19	1	< 0.001
Prematurity (n)	23	-	< 0.001
Cesarean section* (n)	32	10	< 0.01
Neonatal morbidity	16	3	< 0.01
Perinatal mortality	8	-	< 0.01

IUGR : Intra uterine growth restriction
* : Previous cesarean sections excluded

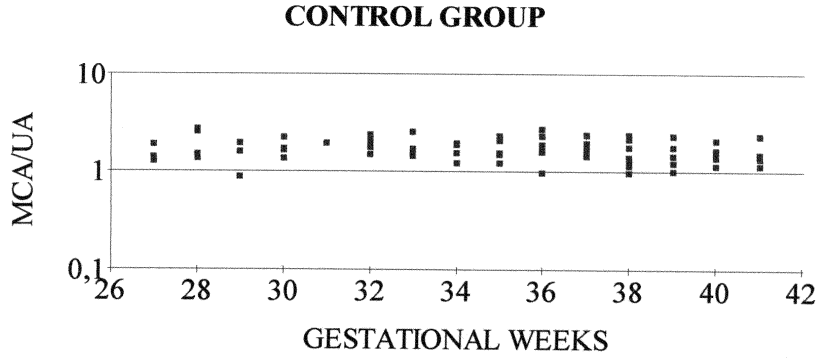

Figure 1: Distribution of the ratio of MCA PI / UA PI in the control group during the third trimester of gestation.

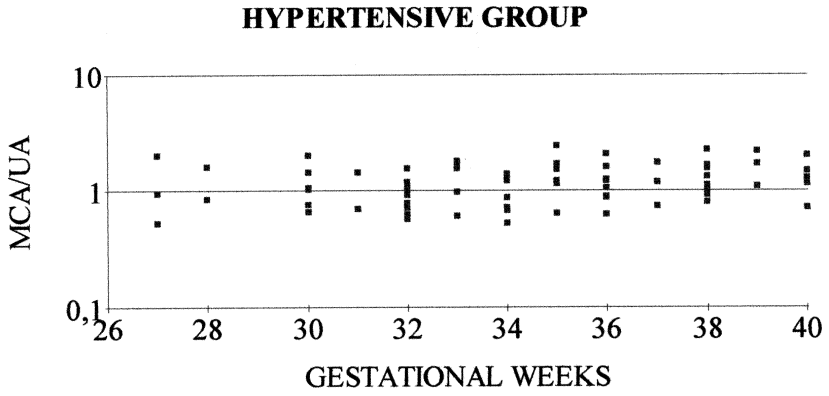

Figure 2: Distribution of the ratio of MCA PI / UA PI in the hypertensive group during the third trimester of gestation.

Table 4. Comparison of Standard Diagnostic Tests in the Prediction of Complications in Hypertensive Proteinuric Pregnancies

	UA PI %	MCA PI %	MCA/UA %
Sensitivity	41	48	57
Specificity	82	82	90
Positive Predictive Value	72	75	87
Negative Predictive Value	56	59	65

DISCUSSION

Proteinuric hypertension in pregnancy (preeclampsia) is one of the leading causes of IUGR and related complications (14). The IUGR fetus has a higher risk for adverse perinatal outcome than normal fetuses and who are constitutionally small. Doppler techniques are widely used for the prediction of these entities (15). The Doppler assessment of the uteroplacental circulation is defined not to be always clinically useful test for predicting preeclampsia or IUGR even in high-risk pregnancies, in the second trimester of the pregnancy (16,17). But umbilical and middle cerebral artery Doppler findings may give some information while other fetal vessel results are still normal. A systemic disease like preeclampsia or signs of IUGR can be seen after those abnormal results. In severe cases this phenomenon appears as early as 20-24 gestational weeks, but in mild cases it is generally seen after 26-32 gestational weeks (15). In growth restricted fetuses, high PI values on UA and low PI values on MCA have been demonstrated (18). We also found similar results in established cases of preeclampsia or eclampsia (Table 2).

Normal development of the placenta exhibits increased diastolic component on umbilical flow velocity waveforms with advancing gestation. This is the result of decreased placental resistance (19). In placental insufficiency, it is said that the placental resistance is increased (19,20) in the other word, not decreased. In some experimental models it is shown that increased umbilical artery Doppler indices may result from either bradycardia or reduced fetal blood pressure instead of a change only in placental resistance (21-23). This increase is reflected by low diastolic component in umbilical artery spectrum and may be worse by beco-

ming absent or reversed. These fetuses are candidates for neonatal morbidity and mortality. But the umbilical artery Doppler findings are not sufficient to precise the delivery timing alone (15). In our study, absent end diastole in fetal arteries was present in 9 cases and all of them were in the hypertensive group. The positive predictive value for UA PI in the detection of hypertensive cases was 72% with the cutoff value, 1.24.

The middle cerebral artery is the preferred vessel to the assessment of fetal cerebral circulation (24). In the third trimester of the pregnancy, MCA PI decreases gradually until term in normal fetuses especially after 33rd gestational week (25). It has been also shown that there is an increase in blood flow to the brain in the IUGR fetuses (24,26). In fetuses with augmented brain blood flow so called "redistribution of blood flow" or "brain sparing effect" (27,28), hypoxemia has been shown in fetal blood samplings (3). We found the brain sparing effect (cutoff value : 1.27) in 52 cases with a positive predictive value of 75% for the hypertensive group in our study.

MCA Doppler examinations can predict fetal jeopardy earlier than conventional fetal well-being tests (5,10,29,30) and provide useful information about perinatal outcome, especially in the high-risk pregnancies (31-32). However the sensitivity of this prediction may be low (24, 28). We also found as low as 30% sensitivity for MCA PI in IUGR cases. Furthermore, MCA PI may be influenced negatively by uterine contractions, fetal tachycardia, fetal anemia, intrauterine transfusion, ductal constriction, hypoxemia, acidemia and positively by fetal bradycardia, oligohydramnios, fetal head compression, therapeutic amniocentesis, sustained hypoxemia with acidemia (15).

In clinical practice, it is very important to know the circumstances of placental and cerebral circulation. If increased placental vascular resistance and decreased cerebral vascular resistance may be reflected by a single parameter, clinician can be easily oriented for fetal surveillance. Several studies have reported that a Doppler parameter that reflects both the umbilical and cerebral arterial features may be useful for identifying those cases (6,10, 27). The sensitivity, specificity, positive and negative predictive values of MCA/UA for detecting our hypertensive proteinuric cases were all higher than that of MCA PI or UA PI alone.

While umbilical and middle cerebral artery pulsatility indices decrease with advancing gestation, the ratio on PI between these two arteries remains stable after 30 weeks of gestation and the cutoff value for this ratio is accepted 1.08 at 2SD (10). On the other hand, Arias et al found a ratio of 1.04 at cerebral-umbilical resistance index (6).In the same way, we found that there was no correlation between MCA/UA and advancing gestational weeks in normal pregnancies, and our cutoff value of MCA/UA was 1.21 at 1SD.

According to Gramellini et al (10) and Arduini et al (11), assessment of umbilical artery is better than middle cerebral artery in predicting poor perinatal outcome. But the same authors marked that the MCA/UA provide better information in predicting perinatal outcome when compared with umbilical or middle cerebral artery Doppler indices alone. On the other hand, it has been supposed that identification of brain sparing effect in growth restricted fetuses may be helpful only in pregnancies <34 weeks (33). In our study group, umbilical artery PI results showed better information than middle cerebral artery PI results for the prediction of fetal mortality. The cerebral to umbilical ratio (<1.2) was found more sensitive, specific and predictive than umbilical artery and middle cerebral artery PI results alone in hypertensive proteinuric pregnancies.

CONCLUSION

We conclude that measurement of both umbilical and middle cerebral blood flow waveforms by duplex Doppler ultrasonography may be useful to assess the complications in hypertensive proteinuric pregnancies at the third trimester of pregnancy. Cerebral to umbilical ratio seems to be better than either middle cerebral artery or umbilical artery PI values alone.

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