Middle Cerebral/Umbilical Artery Resistance Index Ratio as Sensitive Parameter for Fetal Well-being and Neonatal Outcome in Patients with Preeclampsia: Case-control Study

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Aim	To evaluate the accuracy of middle cerebral/umbilical artery resistance index (C/U RI) ratio in predict- ing acidemia and low Angar score at 5 minutes after birth in the infants of women with preeclampsia
Methods	This prospective case-control study performed at Kasr El Aini University Hospital included 50 pregnant women with preeclampsia with or without intrauterine growth restriction (IUGR). Thirty women with uneventful pregnancies, matched for age, parity, and gestational age, served as controls. Ultrasound and Doppler studies were carried out to estimate fetal weight (EFW) and determine fetal biophysical profile and resistance indices of the middle cerebral and umbilical arteries. C/U RI < 1.0 was considered abnormal. Apgar scores were assessed at 5 minutes after birth, and fetal cord blood sampling to determine blood pH was done immediately after delivery. Apgar score < 6 at 5 minutes, neonatal acidemia (pH < 7.2), and/or neonatal admission to neonatal intensive care unit (NICU) indicated neonatal morbidity
Results	There were no significant differences in fetal biophysical profile, middle cerebral artery RI, or umbilical artery RI between the fetuses of women with preeclampsia and those in the control group. C/U RI < 1.0 was found in significantly more fetuses of women with preeclampsia than in their controls (0.7 ± 0.3 and 1.3 ± 0.7 , respectively; $P < 0.001$). In the preeclampsia group, C/U RI was abnormal in 32 out of 38 fetuses with IUGR, and in only 5 out of 12 of fetuses without IUGR. Neonatal acidemia was found in 30 out of 38 newborns with IUGR and in 3 out of 12 of newborns without IUGR. Preeclampsia and C/U RI < 1.0 carried a relative risk of 1.4 for neonatal morbidity (neonatal academia pH < 7.2, 5-minute Apgar score < 6, and/or admission to NICU). C/U RI had 64.1% sensitivity, 72.7% specificity, 89.2% positive predictive value, and 36.3% negative predictive value for neonatal morbidity.
Conclusion	There was a strong correlation between the C/U RI and neonatal outcome in women with pre- eclampsia. C/U RI < 1.0 may be helpful in the identification of newborns at risk of morbidity, irrespec- tive of whether they are small or appropriate for their gestational age.

Preeclampsia is a pregnancy-specific syndrome characterized by reduced organ perfusion secondary to vasospasm and endothelial pathophysiology. The reported incidence of preeclampsia is 5-8% (1). This condition is a leading cause of maternal mortality and is responsible for considerable perinatal morbidity and mortality (2). As a result of impaired uteroplacental blood flow, manifestations of preeclampsia may be seen in the fetal placental unit. These include intrauterine growth restriction (IUGR), oligohydramnios, placental abruption, and non-reassuring fetal status found on ante-partum surveillance by Doppler ultrasound (3,4). Ante-partum assessment is based on the premise that identification and timed delivery of the hypoxic and acidotic fetus will prevent intrauterine fetal death and decrease the risk of long-term adverse effects.

High flow resistance in the capillaries of the terminal villi leads to a low end-diastolic velocity in the umbilical artery and consequent hypoxia (5). As a result of the prolonged fetal hypoxia, circulatory adaptation occurs in the form of cerebral vasodilatation, resulting in the redistribution of the cardiac output to provide an adequate oxygen supply to the brain. These changes, which help fetus to adapt to a hostile environment, may correlate with fetal neonatal health.

The purpose of this study was to assess the accuracy of the middle cerebral to umbilical artery resistance index ratio (C/U RI) in predicting fetal outcome in pregnancies complicated by preeclampsia with or without IUGR and to find the sensitivity of C/U ratio in ante-partum evaluation of fetal well-being in high-risk pregnancies. Moreover, an additional question is whether abnormal C/U RI ratio can predict fetal acidemia and low Apgar score at 5 minutes.

Patients and Methods

Fifty pregnant women with preeclampsia with or without IUGR were enrolled in casecontrol study. Thirty pregnant women with uneventful pregnancies, matched for age, parity, and gestational age, served as controls. The women were recruited consecutively at the Cairo University Hospital from June 2002 to June 2003.

Inclusion Criteria

Pregnant women with viable singleton pregnancies who did not have any obstetric or other morbidity except for preeclampsia were included in the study. Preeclampsia was diagnosed according to the criteria of the International Society for the Study of Hypertension in Pregnancy: a previously normotensive woman with two repeated (4-h apart) diastolic blood pressure measurements of ≥90 mm Hg after the 20th week of pregnancy, along with proteinuria of \geq 300 mg/L in 24-hour urine (6). The pregnancy could be complicated by IUGR, defined as ultrasound-estimated fetal weight of less than the 10th percentile for gestational age. A pregnant woman qualified for the study if she received no medication during the pregnancy apart from iron supplements, was not in

active labor, and delivered by elective cesarean section for any indication but fetal distress.

The control group consisted of 30 women with uneventful viable singleton pregnancies after 28 weeks of gestation. The inclusion criteria for women in the control group were the same as for the women with preeclampsia: no medications during the pregnancy except for iron supplements, not in active labor, and delivery by elective cesarean section for any indication but fetal distress. Both groups of women underwent detailed history taking and physical examination.

Clinical Assessment

Laboratory testing included complete blood count, liver function tests, and kidney function tests. Ultrasound and Doppler studies were carried out to determine composite ultrasound gestational age, estimated fetal weight (EFW), fetal biophysical profile (7), as well as umbilical and middle cerebral resistance index Doppler studies. Gestational age and fetal weight were determined on the basis of fetal biparietal diameter, abdominal circumference, and femur length. Fetal weight was estimated according to Haddlock et al (8). Fetal biophysical profile included fetal breathing, movements, tone fetal tonus, amount of amniotic fluid, and non-stress test (7). IUGR was defined as estimated fetal weight of less than the 10th percentile for gestational age, according to Sabbugha and Minague growth curves (9). The ultrasound machine used was Elegra (Siemens, Munich, Germany), with a Doppler unit and a 3.5 MHz convex linear probe. The output power of 50 mW/cm² was used, and the high-pass filter was set to 100 Hz. Umbilical artery Doppler resistance index was estimated on a free loop of cord. Waveforms of good quality were collected and analyzed in the absence of fetal breathing movements; on average, 3 separate readings were performed. During the examination, the women were in a semi-recumbent position with the head and chest slightly elevated. The recording was performed during periods of fetal apnea, because of a potential effect of fetal breathing movements on waveform variability. For measurements of the middle cerebral artery resistance index, an axial view of the fetal head was obtained at the level of the cerebral peduncles. Color Doppler was used to visualize the circle of Willis. The Doppler sample volume was placed within 1 cm of the origin of the middle cerebral artery that was easily identified as a major branch running in anterolateral direction from the circle of Willis towards the lateral edge of the orbit. For the waveform analysis, maximum and minimum values of the velocity waveforms on the frozen image were measured by use of electronic calipers of the machine. The Pourcelot resistance index (systole-diastole/dystole) was calculated by a built-in microcomputer (10). The C/U RI was estimated based on the two previous results, with a cut-off value of 1.0. Only C/U RIs < 1.0 were considered abnormal (11). The obstetrician in charge of the patients was unaware of their C/U RIs.

Our study included only pregnant women who delivered by cesarean section. In all cases, the time from skin incision to delivery was less than 10 minutes. Immediately after delivery, a segment of the umbilical cord was double-clamped and blood was collected separately from the artery and vein into heparinized plastic syringes. The blood sample was then transported on ice for acid-base analysis, performed on a model 178 automatic pH blood gas analyzer. All fetal blood pH measurements were done within 5 minutes of blood collection. Apgar scores were determined at 5 minutes after birth. Neonatal morbidity was established if Apgar score < 6 at 5 minutes and neonatal acidemia of pH < 7.2 were present and/or newborn was admitted to the neonatal intensive care unit (NICU).

Statistical Analysis

Statistical analysis of categorical variables was performed by chi-square test with continuity correction or Fisher exact test when appropriate. The nonparametric Mann-Whitney U-test (for ordinal data) and Spearman rank correlation were used to determine the degree of correlation between C/U ratio and cord blood pH. Sensitivity, specificity, and positive and negative predictive values were calculated for the diagnostic characteristics used to predict the outcome. All *P* values were two-tailed, and *P* < 0.05 was considered statistically significant. The SPSS/PC+ statistical package (SPSS Inc. Chicago, IL, USA) was used for all analyses.

Results

There were no significant differences between women with preeclampsia and their controls in age, parity, and gestational age (Table 1). The mean systolic/diastolic blood pressure was significantly higher in women with preeclampsia $\ensuremath{\text{Table 1.}}$ Clinical characteristics of women with preeclampsia and their controls*

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Parameter	with preeclampsia (n=50)	controls (n=30)
Age (mean±SD, years)	24.8±6.1	26.3±6.9
Parity (mean±SD)	0.4±0.6	1.1±1.2
Gestational age (mean±SD, weeks)	36.9±2.5	38.8±1.2
Blood pressure (mean±SD, mm Hg):		
systolic	156.8±13.3	113.7±10.6
diastolic	104.7±9.3	74.3±6.1
Pregnancies with IUGR (n, %)	38 (76.0)	0
Neonatal birth weight (mean±SD, g)	1,877±562	3,346±261
5-min Apgar score (mean±SD)	5.9±1.8	8.1±0.8
NICU admission (n, %)	33 (66.0)	0
Cord blood pH <7.2 (n, %)	33 (66.0)	0

*Abbreviations: IUGR – intrauterine growth restriction; NICU – neonatal intensive care unit.

than in the controls $(156.8 \pm 13.3/104.7 \pm 9.3 \text{ vs} 113.7 \pm 10.6/74.3 \pm 6.1 \text{ mm Hg}; P=0.02$, Mann-Whitney U-test). Out of 50 women with preeclampsia, 38 had pregnancies complicated by IUGR and 33 delivered neonates with 5-minute Apgar score of < 6 who were admitted to NICU.

There was no significant difference between the preeclampsia and control group in any of the performed fetal measurements (fetal biophysical profile, middle cerebral artery RI, or umbilical artery RI) except for the C/U ratio (Table 2). In women with preeclampsia, abnormal C/U RI was found in 32 out of 38 cases with IUGR and in only 5 out of 12 of those without IUGR (Table 3). Neonatal acidemia was noted in 30 out of 38 newborns with IUGR and in 3 out of 12 of those without IUGR. Astonishingly, there was no significant

Table 2. Fetal well-being tests performed in pregnant women with preeclampsia and their controls

	Pregnant women		
Fetal parameter*	with preeclampsia (n=50)	controls (n=30)	
Fetal biophysical profile† (mean±SD)	6.2±1.8	8.8±0.2	
Middle cerebral artery RI (mean±SD)	0.7±0.1	0.7±0.1	
Umbilical artery RI (mean±SD)	0.7±0.1	0.6±0.1	
Abnormal C/U RI ratio <1.0 (n, %)	37 (74.0) [‡]	0	

*Abbreviations: RI - resistance index; C/U RI - middle cerebral/umbilical artery resistance index.

†Maximum score is 10.

⁺ ‡P<0.001, Fisher exact test

Table 3. Comparison between fetuses with and without intrauterine growth restriction (IUGR) in pregnant women with preeclampsia

	Fetuses		
Parameter*	with IUGR (n=38)	without IUGR (n=12)	
Cord blood pH <7.2 (n, %)	30 (78.9)	3 (25.0)	
Middle cerebral artery RI (mean±SD)	0.67±0.02	0.68±0.10	
Umbilical artery RI (mean±SD)	0.73±0.04	0.69±0.04	
Abnormal C/U RI ratio <1.0 (n, %)	32 (84.2)	5 (41.7)	

*Abbreviations: RI - resistance index; C/U RI - middle cerebral/umbilical artery resistance index.

Parameter (cut-off value) No. of women Sensitivity (%) Specificity (%) PPV (%) NPV (%) Overall efficiency (%) R	Tuble - Medsurements performed in so women with precountpaid to predict neonatal doldosis							
	Parameter (cut-off value)	No. of women	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall efficiency (%)	RR
FBP (<7) 13 27.8 26.7 54.7 15.0 26.0 (13/50) 1.02	FBP (<7)	13	27.8	26.7	54.7	15.0	26.0 (13/50)	1.02
UA RI (0.72) 22 53.3 36.4 81.1 30.8 44.0 (22/50) 1.17	UA RI (0.72)	22	53.3	36.4	81.1	30.8	44.0 (22/50)	1.17
MCA RI (0.69) 17 41.0 63.6 80.0 23.3 34.0 (17/50) 1.04	MCA RI (0.69)	17	41.0	63.6	80.0	23.3	34.0 (17/50)	1.04
C/U RI ratio (<1.0) 37 64.1 72.7 89.3 36.4 74.0 (37/50) 1.40	C/U RI ratio (<1.0)	37	64.1	72.7	89.3	36.4	74.0 (37/50)	1.40

able 4. Measurements performed in 50	women with preeclampsia to	predict neonatal acidosis*
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*Abbreviations: PPV – positive predictive value; NPV – negative predictive value; RR – relative risk; FBP – fetal biophysical profile (maximum score is 10); UA RI – umbilical artery resistance index (0.72 indicates high resistance); MCA RI – middle cerebral artery resistance index (0.69 indicates high resistance); C/U RI – middle cerebral/umbilical artery resistance index.

difference in the RIs of the middle cerebral and umbilical arteries between the fetuses with and those without IUGR.

We compared the sensitivity, specificity, positive and negative predictive values, overall efficiency and relative risk of biophysical profile, umbilical artery and middle cerebral artery resistance indices, and the C/U RI for the diagnosis of fetal morbidity (Table 4). Although the values were comparable, the abnormal C/U RI seemed to be the best test for the fetal outcome. Preeclamptic pregnancies with C/U RI <1.0 carried relative risk of 1.4 (95% confidence interval, 1.2-1.7) of neonatal acidemia (pH < 7.2), low 5-minute Apgar score (< 6), and/or admission to NICU. In addition, C/U RI had 64.1% sensitivity and 72.7% specificity to detect fetuses at risk of acidemia, with 89.3% positive and 36.4% negative predictive values.

Discussion

We found that newborns of women with preeclampsia and C/U RI < 1.0 had increased relative risk of neonatal acidemia, low 5-minute Apgar score, and/or admission to NICU. Our study also showed that C/U RI had a better specificity than either middle cerebral or umbilical artery resistance indices as measured by Doppler in predicting poor neonatal outcome. There were significant differences in the umbilical artery resistance index between normal fetuses and those with IUGR. The mean umbilical artery resistance index was significantly higher in the fetuses with IUGR. This was largely a result of a decrease in the amplitude of the end diastolic component of the waveform.

Despite the availability of multiple modalities of ante-partum tests, there is no ideal test for all high-risk fetuses and some ante-partum fetal tests are more appropriate than others, depending on the underlying pathophysiology or the indication for testing. The challenge for prenatal surveillance is to identify those fetuses whose physiological defense mechanisms are compromised, in order to act before decompensation has occurred. Preeclampsia, a condition unique to human pregnancy, is a significant cause of maternal and neonatal morbidity and mortality. IUGR resulting from placental compromise is accompanied by placental vascular damage. The current routine prenatal surveillance tests such as the non-stress test and fetal biophysical profile may not be sensitive or specific enough to detect fetuses with an early compromise (12).

The use of Doppler umbilical waveforms as a fetal surveillance test had gained a wide popularity, especially in high risk cases (13,14). With more advances in Doppler ultrasonography, the fetal cranial circulation became an interesting subject to study, together with the umbilical artery, as it represents the fetal adaptation to changes in the circulation (14). In fetuses with IUGR, resistance indices in all major intracranial arteries are significantly reduced as a response to the increased fetal peripheral vascular resistance, so that the cerebral blood flow is preserved. This phenomenon is called the "brain sparing effect" (15).

Considering that C/U RI reflects not only the circulatory insufficiency of the placenta by alteration in the umbilical resistance index, but also the adaptive changes resulting in modification of the middle cerebral resistance index, it seemed to be a potentially useful tool in predicting adverse perinatal outcome in high risk cases. Our results support the correlation between abnormal fetal C/U RI and adverse perinatal outcome in patients with preeclampsia with or without IUGR.

Some authors reported that C/U RI was more accurate than each of its components in the diagnosis of fetal morbidity and compromise (11,16-18). Others had found that abnormal cerebroplacental resistance index ratio, which is similar to our C/U RI, was associated with a significant increase in perinatal morbidity and mortality in pregnancies at risk of fetal growth restriction (19). They also emphasized that abnormal cerebroplacental ratio was a finding largely confined to preterm infants born at < 34 weeks of gestation (19). Other investigators (20) also showed a correlation between fetal biophysical profile and fetal compromise, although they did not use the same parameters as we did for C/U RI, neonatal pH and definition of fetal morbidity.

The diagnosis of fetal hypoxia is probably more representative of intrauterine pH of fetal blood if the blood sampling is done before labor. To circumvent this possible limitation, we included only infants born by a cesarean section. We believed that cesarean section would not affect the fetal acid base status as vaginal labor would. Other limitation stem from limitations of ultrasound techniques used to measure arterial resistance indices.

In conclusion, we found a strong correlation between the C/U RI and neonatal outcome in cases with preeclampsia, especially in those with IUGR. However, we could not establish the clinical usefulness of C/U RI measurements in evaluation of long-term outcomes of high-risk neonates.

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