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The Value of Middle Cerebral Artery and Umbilical Artery Doppler Indices in Assessment of Fetal Wellbeing and Prediction of Neonatal Outcome in Preeclampsia

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ABSTRACT

Aim of The Study: To evaluate the value of middle cerebral artery and umbilical artery Doppler indices in assessment of fetal wellbeing and prediction of neonatal outcome in pregnant women with preeclampsia.

Patients and Methods: This study included 100 pregnant women with preeclampsia, 50 women with uneventful pregnancies, Ultrasound and Doppler studies were carried out to estimate fetal weight, fetal biophysical profile and resistance indices of the middle cerebral and umbilical arteries. C/U RI <1.0 was considered abnormal. Adverse neonatal outcome was diagnosed when Apgar score <6 at 5 minutes, C.S for fetal distress, stained meconium, abnormal BPP, perinatal death and/or neonatal admission to neonatal intensive care unit.

Results: adverse neonatal outcome in groups A, B and C was significantly correlated to UA-RI and UA-PI. Between the normal and adverse neonatal outcome, in group A, there was a significant difference in UA-RI (P-value = 0.021); in group B, there was a significant difference in UA-RI and UA-PI (P-value <0.001 and P-value <0.001 respectively); and in group C, there was a significant difference in UA-RI and UA-PI (P-value <0.001 and P-value =0.004 respectively). In our study, both absent and reversed diastolic flows were significantly correlated with bad neonatal outcome in the study group (P value <0.001, r-value = 0.428). **Conclusions:** MCA and UA Doppler indices are good utilities for the assessment of fetal wellbeing and prediction of neonatal outcome in pregnant women with preeclampsia.

Keywords: Doppler indices, preeclampsia, neonatal outcome.

INTRODUCTION

Preeclampsia is a major contributor to maternal mortality worldwide and remains a leading cause of perinatal mortality and morbidity, complicating 2–8% of pregnancies **(1)**. Although the precise mechanism through which preeclampsia develops is uncertain, research in the field continues to advance understanding of the underlying pathophysiology. Endothelial cell dysfunction following placentation appears to play a central role in the pathogenesis of the disease **(2)**.

An inadequate invasion of trophoblasts with consequential placental ischemia as a result of insufficiently dilated uterine spiral arteries is thought to be an initial cause in the pathogenesis of pre-eclampsia **(3)**. The current routine prenatal surveillance tests such as the non-stress test and fetal biophysical profile (BPP) may not be sensitive or specific enough to detect fetuses with an early compromise **(4)**. Doppler flow velocimetry of the umbilical and fetal cerebral circulation serves as another modality for the assessment of fetal status. This technique can be helpful in identifying the compromised fetus and could be of clinical value in the differential diagnosis between drug-induced changes in fetal biophysical behavior and those due to fetal compromise **(5)**. As a result of impaired utero-placental blood flow, manifestations of preeclampsia may be seen in 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 **(6)**. On the other hand, IUGR fetuses represent a subgroup of fetuses that have failed to reach their growth potential for various reasons, such as genetic disorders, infection and uteroplacental insufficiency to a degree that may affect the health of the fetus. In other words, IUGR is the pathological counterpart of SGA **(7)**. High flow resistance in the capillaries of terminal villi leads to a low end-diastolic velocity in the umbilical artery and a subsequent hypoxia **(8)**. During chronic fetal hypoxia there is continuous reduction of cerebral vascular resistance resulting in decrease middle cerebral artery resistance index values gradually **(9)**.

The use of Doppler umbilical wave forms as a fetal surveillance test had gained a wide popularity, especially in high risk cases **(10)**. Considering that CPR 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 artery resistance index. It seemed to be a potentially useful tool in predicting adverse perinatal outcome in high risk cases **(11)**.

AIM OF THE WORK

To evaluate the value of middle cerebral artery and umbilical artery Doppler indices in assessment of fetal

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wellbeing and prediction of neonatal outcome in pregnant women with preeclampsia.

PATIENTS AND METHODS

The present study was carried out in the Department of Obstetrics and Gynecology, Police Hospitals, Egypt, during the period from October 2016 to October 2018. The estimated sample was 150 cases, 100 cases as preeclampsia sub grouped into (group A) diagnosed as mild preeclampsia 60 cases and (group B) diagnosed as severe preeclampsia 40 cases, and 50 cases (group C) was a control group. 10 cases dropped out from mild preeclampsia group and 5 cases from severe preeclampsia group. **The study was approved by the Ethics Board of Al-Azhar University.**

Inclusion Criteria

Singleton pregnancy

Gestational age: 34 - 40 weeks.

Preeclampsia, where it will be diagnosed according the criteria of the International Society for the study of hypertension in pregnancy: a previous normotensive woman after the 20th week with

• Diastolic blood pressure measurement of ≥90 mm Hg measured twice or more consecutive occasions ≥4 hours apart.

• Diastolic blood pressure ≥110 mmHg on any one occasion of pregnancy. Along with protienuria of ≥300 mg/L in 24-hour urine or

Two ‘clean-catch-midstream’ or catheter specimens of urine collected ≥4 hours apart with ≥2+ on reagent strip (International society for the study of hypertension in pregnancy, 2002).

Exclusion Criteria

Multiple pregnancies.

Newborns with apparent congenital anomalies

Type 1 IUGR.

Pregnant females with other medical disorders (Diabetes mellitus, history of having cardiac or renal disease).

METHODS

Patients included in the study were subjected to the following:

Verbal consent was obtained from the pregnant women who are included in the study.

Full History Taking Including:

Age. Gestational age, confirmed by the 1st day of her LMP or ultrasound examination during the 1st trimester. Gravidity and Parity.

General examination; included vital signs.Full obstetric examination.

Laboratory Investigations:

- Complete blood picture.
- Fasting and 2 hours postprandial blood sugar.
- Liver function tests.
- Kidney function tests.
- Complete urine analysis.

Ultrasound:

Interval ultrasonographic biometry.

Doppler velocimetry of the UA and MCA will be performed when delivery is indicated.

The indications for delivery included:

Abnormal BPP score (<6/10).

Cessation of fetal growth on interval ultrasonographic biometry.

Gestational age ≥37 weeks.

Deterioration of maternal condition.

Technique of Ultrasonography:

The examination was performed in a supine, slightly left lateral tilted position through the examination to avoid supine hypotension. Ultrasonographic and Doppler flow velocity waveforms (FVW) studies was done with pulsed-wave Doppler and real time color flow localization of the umbilical and middle cerebral arteries [12].

Doppler Study:

- Doppler velocimetry of the UA and MCA was performed using a color Doppler system with curvilinear transabdominal probe. We attempted to achieve an angle close to 0 degrees between the Doppler ultrasound beam and the direction of blood flow in each vessel. In spite of the coiling of the UA, in the appropriately chosen segment of cord it is possible to place the sample gate parallel to the direction of blood flow. The MCA will be visualized near to the point where the internal carotid artery separates into the anterior cerebral artery and the MCA. Measurements were taken during periods of fetal apnea and inactivity. The umbilical artery Doppler indices from at least 3 consecutive waveforms were obtained and averaged to determine the resistance index (RI) and pulsatility index (PI) where [RI = (maximal systolic velocity – least diastolic velocity) / (maximal systolic velocity) and PI = (maximal systolic velocity – least diastolic velocity) / average]. The middle cerebral artery Doppler indices from at least 3 consecutive waveforms were obtained and averaged to determine the resistance index (RI) and peak systolic velocity (PSV). The cerebroplacental ratio (CPR), defined as the MCA-RI divided by the UA-RI, was considered abnormal if <1.0 [13].

Neonatal assessment:

Adverse (or abnormal) perinatal outcome was defined as any perinatal complications such as

Perinatal death

Fetal distress.

Meconium staining of the amniotic fluid.

5-minute Apgar score <7.

Stay in the neonatal intensive care unit for >24 hours.

The perinatal outcomes were correlated to the results of UA and MCA Doppler Indices, and CPR. The accuracy of UA and MCA Doppler Indices and CPR in the prediction of adverse outcome will be calculated.

- The primary outcome variable:

Middle Cerebral Artery Resistance Index (RI) and peak systolic velocity (PSV). Umbilical artery resistance index and pulsatility index (PI).
Middle cerebral/umbilical artery resistance index ratio.

- The secondary outcome variables:

i. Apgar score of the Newborn after 5 min.
ii. Pregnant women with preeclampsia

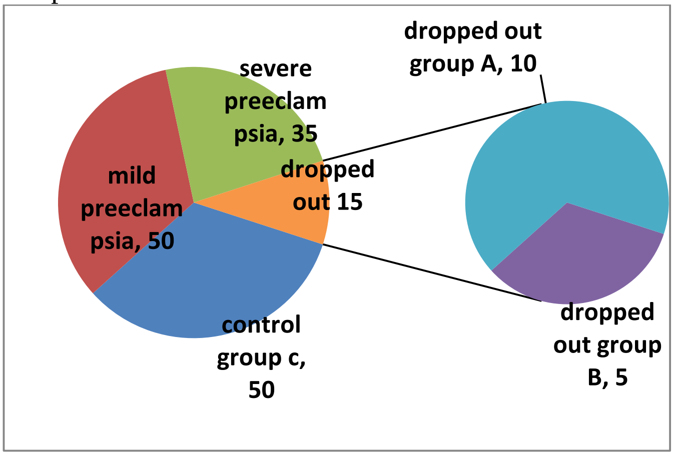
Statistical analysis

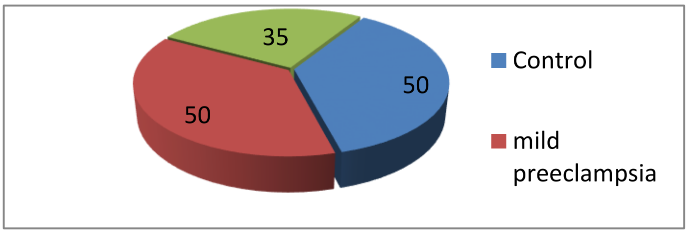
The data were coded, entered and processed on an IBM-PC compatible computer using statistical package for social sciences (SPSS) version 17.

Unpaired Student's t-test was used to assess the statistical significance of the difference between two population means and medians in a study involving independent samples. A P value <0.05 was considered statistically significant (S) while >0.05 statistically insignificant P value <0.01 was considered highly significant (HS) in all analyses.

RESULTS

The present study included 150 pregnant women fulfilling the inclusion and exclusion criteria mentioned before, where 60 of them with mild preeclampsia, 40 with severe preeclampsia, (10 cases dropped out from mild preeclampsia group, 5 cases from severe preeclampsia group) and 50 cases free from any medical disorder by history and clinical examination used as control group. They were admitted to Obstetrics and Gynecology Department, Police Hospitals.





Patients distribution

Table 1: Fetal Characteristic for group A: mild Preeclampsia (n=50)

Fetal Characteristic	Range	Mean ± SD
Doppler study *UR-RI*	**0.49 – 1**	**0.63 ± 0.11**
UA-PI	**0.8 – 3.58**	**1.22 ± 0.49**
MCA-RI	**0.48 – 0.94**	**0.73 ± 0.08**
MCA-PSV, cm/s	**43.78 – 67.43**	**53.91 ± 6.01**
CPR	**0.52 – 1.52**	**1.19 ± 0.23**
UA Doppler wave pattern Absent diastolic flow	**2 (4 %)**	
Gestational age, weeks	**34 – 39.2**	**37.21 ± 1.32**
Birth weight, g	**2700 – 3600**	**2986 ± 397.4**
Neonatal Outcome	**value**	
Normal	**42 (84%)**	
Adverse	**8 (16%)**	
Stay in the NICU for >24 hours	*4*	
Perinatal death	*1*	
Cesarean section for fetal distress	*2*	
5-minute Apgar score <7	*1*	
Apgar score 5 min, /10	**6 – 10**	**10 (median)**

Table 2: Fetal Characteristic for group B: Severe Preeclampsia (n=35)

Fetal Characteristic	Range	Mean ± SD
Doppler study *UR-RI*	**0.68 – 1**	**0.85 ± 0.12**
UA-PI	**1,21 – 3.36**	**2.15 ± 0.64**
MCA-RI	**0.32 – 0.84**	**0.57 ± 0.14**
MCA-PSV cm/s	**53.34 – 73.76**	**65.14 ± 6.21**
CPR	**0.38 – 1.17**	**0.73 ± 0.24**
UA Doppler pattern	**value** **7 (20%)**	
Reversed diastolic flow	**2 (16%)**	
Gestational age, weeks	**34 – 38.4**	**35.31 ± 1.32**
Birth weight, g	**2500 – 3200**	**1903 ± 349.79**
Neonatal Outcome	**value**	
Normal	**6 (16%)**	
Adverse	**29 (84%)**	
Stay in the NICU for >24 hours	*25*	
5-minute Apgar score <7	*18*	
Perinatal death	*3*	
Apgar score 5 min, /10	**0 – 10**	**7 (median)**

Table 3: Fetal Characteristic for group C: Control cases (n=50)

Fetal Characteristic	Range	Mean ± SD
Doppler study		
UR-RI	**0.48 – 0.82**	**0.61 ± 0.09**
UA-PI	**0.78 – 1.44**	**1.06 ± 0.16**
MCA-RI	**0.68 – 0.82**	**0.75 ± 0.03**
MCA-PSV, cm/s	**46.91 – 67.8**	**57.38 ± 4.96**
CPR	**0.84 – 1.65**	**1.25 ± 0.19**
Gestational age, weeks	**37 – 39.8**	**38.48 ± 0.6**
Birth weight, g	**3000 – 3700**	**3358 ± 151.54**
Neonatal Outcome		**value**
Normal		**32 (64%)**
Adverse		**18 (36%)**
Meconium staining of the AF		*11*
5-minute Apgar score <7		*10*
Cesarean section for fetal distress		*6*
Apgar score 5 min, /10	**5– 10**	**9 (median)**

UA-RI: Umbilical Artery Resistance Index, UA-PI: Umbilical Artery Pulsatility Index, MCA-RI: Middle Cerebral Artery Resistance Index, MCA-PSV: Middle Cerebral Artery Peak Systolic Velocity, CPR: Cerebro-Placental Ratio, UA: Umbilical Artery, NICU: Neonatal Intensive Care Unit. AF: Amniotic Fluid.

Adverse neonatal outcome in groups A, B and C was significantly correlated to UA-RI and UA-PI (Group A: P-value <0.001, P-value = 0.0116; Group B: P-value <0.009, P-value = 0.025; Group C: P-value <0.001, P value<0.001 respectively)

Between the normal and adverse neonatal outcome, in group A, there was a significant difference in UA-RI (P-value = 0.021); in group B, there was a significant difference in UA-RI and UA-PI (P-value <0.001 and P-value <0.001 respectively); and in group B, there was a significant difference in UA-RI and UA-PI (P-value <0.001 and P-value =0.004 respectively).

In groups A, B and C r-value of UA-RI had relatively higher values than other Doppler parameters, with a significant correlation with the adverse neonatal outcome (r-value =0.537, 0.631 and 0.789 respectively)

Difference between Groups:

A and C (Mild preeclampsia and control group) Different characteristics of Group A and control Group (Group C), showed significant correlation with the BMI of the pregnant women (P-value <0.001). Data showed that group A was less likely to be primigravida with no significant difference (RR = 0.657, P-value = 0.209). On the other hand, they were more likely to be multigravida with no significant difference (RR = 1.228, P-value = 0.203). Pregnant women age had no significant difference between the 2 groups (P-value = 0.076).

There was a significant correlation between the two groups concerning the gestational age and birth weight (both with P-value < 0.001). Normal neonatal outcome, more likely to occur with group A, with no significant difference (RR = 1.295, P-value = 0.0562), however the adverse outcome less likely to occur, with no significant difference (RR =0.451, P-value = 0.065) (Table 4)

Table 4: Comparison of different characteristic between group A and C

Characteristic	Group A n:50	Group C n=50	RR	P-value	Significance
Age, years old	30.32 ± 6.05 (19 – 42)	27.95 ± 5.72 (21 – 40)		>0.05	NS
BMI, kg/m ^{2}	31.18 ± 3.84 (24.7 – 38.6)	27.96 ± 2.61 (22.8 – 33.6)		***<0.001****	
Parity					
Primigravida	**13 (26%)**	**20 (40%)**	0.657	>0.05	NS
Multigravida	**37 (74%)**	**30 (60%)**	1.228		
Gestational age, weeks	37.21 ± 1.32 (34 – 39.2)	38.48 ± 0.6 (37 – 39.8)		***<0.001****	
Birth weight, g	2986 ± 397.4 (2700 – 3600)	3358 ± 151.54 (3000 – 3700)		***<0.001 ****	
Normal	**42 (84%)**	**32 (64%)**		>0.05	NS
Adverse	**8 (16%)**	**18 (36%)**	0.451		

RR: Relative Risk, P-value: Value of Probability, NS: No Significant difference,
*: Statistically Significant difference (P-Value <0.05), BMI: Body Mass Index

B and C: (Severe preeclampsia and control group)

Different characteristics of group B and group C showed significant correlation with the BMI of the pregnant women (P value < 0.001). Data showed that group B was more likely to be primigravida with no significant difference (RR = 1.053, P-value = 0.877).

On the other hand, they were less likely to be multigravida with no significant difference (RR = 0.965, P-value = 0.879). Pregnant women age had no significant difference between the 2 groups (P-value = 0.303). There was a significant difference between the two groups concerning the gestational age and birth weight (both with P-value < 0.001).

Normal neonatal outcome, was less likely to occur with group B, with significant difference (RR = 0.324, P-value = 0.014), however the adverse outcome was more likely to occur, with significant difference (RR= 2.256, P-value < 0.001) **(Table 5)**

Table 5: Comparison of different characteristic between group B and C

Characteristic	Group B n = 35	Group C n = 50	RR	P-value	Significance
Age, years old	29.74 ± 6.31 (21 – 40)	27.95 ± 5.72 (21 – 40)		>0.05	NS
BMI, kg/m ^{2}	32.11 ± 3.27 (25.4 – 36.4)	27.96 ± 2.61 (22.8 – 33.6)		***<0.001****	
Parity					
Primigravida	**15 (42%)**	**20 (40%)**	1.053	>0.05	NS
Multigravida	**20 (58%)**	**30 (60%)**	0.965		
Gestational age, weeks	35.31 ± 1.32 (34 – 38.4)	38.48 ± 0.6 (37 – 39.8)		***<0.001****	
Birth weight, g	1903 ± 349.79 (2500 – 3200)	3358 ± 151.54 (3000 – 3700)		***<0.001 ****	
Neonatal Outcome					
Normal	**6 (16%)**	**32 (64%)**	0.324	***<0.001****	
Adverse	**29 (84%)**	**18 (36%)**	2.256		

In general, UA-wave pattern, of either absent or reversed diastolic flow, was highly significant correlated to the adverse neonatal outcome with P-value <0.001 and r-value= 0.428 **(Table 6)**.

Table 6: The correlation between adverse neonatal outcome and UA-wave pattern

	r-value	P-Value
Adverse neonatal outcome and UA-wave pattern	0.428	***<0.001****

DISCUSSION

Despite the availability of multiple modalities of ante-partum tests, there is no ideal test for all high-risk pregnancies and some tests are more appropriate than others, depending on the underlying pathophysiology and the indication for testing [(6)]**.** However, fetal Doppler indices provide information that is not readily obtained from more conventional tests of fetal well-being [(14)]**.** The present study was designed to correlate the perinatal outcomes to the results of UA, MCA Doppler indices, and CPR. The accuracy of UA, MCA Doppler indices and CPR in the prediction of adverse outcome were calculated, as primary outcome variable. The current study, also, aimed to explore the possible risk factors for pregnant women with mild and severe preeclampsia. The current study included 150 women were categorized into 3 groups, as mentioned before. As regarding the results, adverse neonatal outcome in groups A, B and C was significantly correlated to UA-RI and UA-PI (Group A: P-value <0.001, P-value = 0.0116; Group B: P-value <0.009, P-value = 0.025; Group C: P-value <0.001, P value<0.001 respectively). Between the normal and adverse neonatal outcome, in group A, there was a significant difference in UA-RI (P-value = 0.021); in group B, there was a significant difference in UA-RI and UA-PI (P-value <0.001 and P-value <0.001 respectively); and in group B, there was a significant difference in UA-RI and UA-PI (P-value <0.001 and P-value =0.004 respectively). With the present study, studies showed a significant correlation between umbilical artery Doppler indices and adverse perinatal outcome in patients with preeclampsia. They concluded that an abnormal Doppler umbilical artery waveform is associated with poor perinatal outcome and is a strong predictor of perinatal mortality [(15)]**.** There was significant neonatal morbidity compared with those with normal velocimetry *(p < 0.05)* especially those with severe preeclampsia [(16)]**.** With our study also, a study done in 1991, showed that value of the Doppler examination of UA-RI in predicting fetal distress was applicable to appropriately grown as well as small for gestational age fetuses [(17)]. Doppler velocimetry (UA-RI and UA- PI) is an effective method of fetal surveillance in pregnancies complicated by preeclampsia [(18-19)]. In groups A, B and C r-value of UA-RI had relatively higher values than other Doppler parameters, with a significant correlation with the adverse neonatal outcome *(r-value =0.537, 0.631 and 0.789 respectively)*. It agrees with study done in 2006, stated that UA-RI proved to be an earlier indicator of fetal compromise before any fetal distress becomes obvious [(20-21)]**.** Doppler investigation of the fetal circulation not only plays an important role in monitoring of the growth restricted fetuses but also helps in detecting fetal compromises early in intrauterine growth restriction fetuses and thereby helps to determine the optimal time for delivery [(22)]**.**

In cases where the end diastolic flow was absent or reversed in the umbilical artery flow is often indicative of acute fetal distress and unfavorable prognosis. Reverse end diastolic flow in the umbilical artery was always associated with the intrauterine death of the fetus. The studies' results confirmed the validity of Doppler ultrasonography in the cases of preeclampsia and/or fetal growth restriction and that UA-wave pattern being an informative parameter of perinatal outcomes independent of gestational age [(23-26)]. Elevated umbilical artery indices are associated with higher rates of maternal and fetal disease UA-PI >95th centile for gestation was associated with statistically higher rates of SGA infants [(27)]**.**

In our study, birth weight was highly significantly different between the two preeclampsia groups and the control group (P-value <0.001), also cesarean section had highly significant difference between normal and adverse neonatal outcome, in different groups. It agrees with a study showed that an UA-PI > 1.2 was associated with statistically higher rates of infants that were SGA. Also; high cesarean delivery rates were correlated with an UA-PI > 1.2. However, the Doppler waveforms at term had low prognostic value for predicting neonatal acidosis or decreased Apgar scores which disagree with our results in control group C. This study was performed in larger study group (365 cases) with gestational age reached up to 41 weeks [(28)]**.** In agreement with group C, a study done in 2010 concluded that fetuses, of no maternal or fetus risk, with abnormal UA Doppler suffered more morbidity and mortality compared to those with normal UA Doppler [(29)]**.** In groups A and C, there was no significant difference in MCA-RI *(P-value = > 0.05).* Fetuses examined close to labor presented more intense Doppler changes in the cerebral arteries with a significant reduction of the MCA RI. This reduction was larger in the MCA. Before the onset of term labor, the fetal cerebral flow presents an additional reduction of impedance, which is more intense in the MCA system [(30)]**.** It agrees with that of control group (group C), a study showed that abnormal middle cerebral artery Doppler had limited predictive accuracy for compromise of fetal/neonatal wellbeing. High quality primary research or individual patient data meta-analysis looking at this test in combination with other tests is required [(31)]**.** However, in another study, concerning MCA RI, no difference was seen among the groups of fetuses who maintained diastolic flow in the UA. However, MCA RI was lower when the UA diastolic flow was absent. Decreasing MCA impedances only when UA flow is severely affected [32]. Another study showed that the umbilical and cerebral artery Doppler is a relatively poor predictor of neonatal outcome. It seems that neonatal birth weight is the best predictor of neonatal outcome in high-risk pregnancies. Here, in the present study; in birth weight in the groups A and B, there was a significant difference between the normal and adverse neonatal outcome (P-value = 0.0497 and <0.001, respectively). There was a significant correlation between CPR and APGAR-5 (p = 0.003). We found a significant correlation between neonatal birth weight and APGAR-5 (p = 0.001) [33].

CONCLUSION AND RECOMMENDATIONS

MCA and UA Doppler indices are good utilities for the assessment of fetal wellbeing and prediction of neonatal outcome in pregnant women with preeclampsia. CPR is a strong parameter to predict the adverse neonatal outcome in pregnant women with preeclampsia. Abnormal UA wave pattern can predict an adverse neonatal outcome.

BMI of the pregnant women one of the important risk factors for developing preeclampsia in pregnant women.

Further studies are needed on a larger scale, with introducing new Doppler measurements to different fetal vessels, and to measure different indices, which might be valuable to predict the adverse neonatal outcome in pregnant women with preeclampsia.

REFERENCES

1. **Steegers EA, von Dadelszen P, Duvekot JJ *et al.* (2010):** Pre- eclampsia. Lancet, 376(9741):631-44
2. **Redman CW, Sargent IL (2005):** Latest advances in understanding preeclampsia. Science, 308:1592–4.
3. **Kang A, Struben H (2008):** Pre-eclampsia screening in first and second trimester. Ther. Umsch., 65(11): 663-6.
4. **Yoon BH, Romero R, Roh CR *et al.* (1993):** Relationship between the fetal biophysical profile score, umbilical artery Doppler velocimetry, and fetal blood acid-base status determined by cordocentesis. Am. J. Obstet. Gynecol., 169(6):1586-94
5. **Harman AL, Barchar AA (2003):** Distribution of circulation in the normal and asphyxiated fetal primate. Am. J. Obstet. Gynecol., 108: 956-69.
6. **ACOG (American College of Obstetricians and Gynecologists) (2002):** Diagnosis and management of preeclampsia and eclampsia. Practice Bulletin No. 33. Obstet. Gynecol., 99:159–167.
7. **Bamberg C, Kalache KD (2004)**: Prenatal diagnosis of fetal growth restriction. Semin. Fetal Neonatal Med., 9(5):387-94.
8. **Weiner Z, Farmakides A, Schulman H *et al.* (1994):** Central and peripheral hemodynamic changes in fetuses with absent end diastolic velocity in umbilical artery:correlation with computerized FHR pattern. Am. J. Obstet. Gynecol., 170(2):509-15.
9. **Mimica M, Pejkovic L, Furlan I *et al.* (1995):** Middle cerebral artery velocity waveforms in fetuses with absent umbilical artery end- diastolic flow. Biol. Neonate, 67(1):21-5.
10. **Alfirevic Z, Nelison JP (1995):** Doppler ultrasonography in high risk pregnancies:systemic review with meta-analysis. Am. J. Obstet. Gynecol., 172:1379-87.
11. **Ebrashy, Azmy O and Ibrahim M (2005):** Middle cerebral umbilical artery resistance index ratio as sensitive parameter for fetal well-being and neonatal outcome in patients with the eclampsia. Case Control Study. Croat. J. Med. J., 46 (5): 826-831.
12. **Chirit Y, Caubel P, Herrero R *et al.* (2000):** Effect of maternal dexamethasone administration on fetal Doppler flow velocity wave forms. Br. J. Obstet. Gynecol., 107(4):501-7.
13. **Arias F (1994):** Accuracy of the middle-cerebral-to-umbilical-artery resistance index ratio in the prediction of neonatal outcome in patients at high risk for fetal and neonatal complications. Am. J. Obstet. Gynecol., 171:1541-5.
14. **Harrington K, Kurdi W, Acquilina J *et al.* (2000):** A prospective manegment study of slow release asprin in the palliation of uteroplacental insufficiency predicted by uterine artery Doppler at 20 weeks ultrasound. Obstet. Gynecol., 15:13-18.
15. **Bilardo CM, Wolf H, Stigter RH *et al.* (2004):** Relationship between monitoring parameters and perinatal outcome in severe, early intrauterine growth restriction. Ultrasound Obstet. Gynecol., 23(2): 119-25**.**
16. **Arauz JF, León JC, Velásquez PR *et al.* (2008).** Umbilical artery Doppler velocimetry and adverse perinatal outcome in severe pre-eclampsia. Ginecol. Obstet. Mex., 76(8):440-9.
17. **Pattinson RC, Dawes G, Jennings J *et al.* (1991):** Umbilical artery resistance index as a screening test for fetal well-being. I: Prospective revealed evaluation. Obstet. Gynecol., 78(3):353-8.
18. **Ivanov S, Mikhova M, Sigridov I *et al.* (2006):** Doppler velocimetry in patients with preeclampsia. Akush. Ginekol. (Sofiia), 45(2):3-9.
19. **Tchirikov M, Strohner M, Förster D *et al.* (2009):** A combination of umbilical artery PI and normalized blood flow volume in the umbilical vein: venous-arterial index for the prediction of fetal outcome. Eur. J. Obstet. Gynecol. Reprod. Biol., 142:129-133.
20. **Nguku SW, Wanyoike-Gichuhi J and Aywak AA (2006):** Biophysical profile scores and resistance indices of the umbilical artery as seen in patients with pregnancy induced hypertension. East Afr. Med. J., 83(3):96-101.
21. **Korbelak T, Ropacka-Lesiak M and Breborowicz G (2012):** Doppler blood flow velocimetry in the umbilical artery in uncomplicated pregnancy. Ginekol. Pol., 83(1):38-45.

22. **Roy A, Mukherjee S, Bhattacharyya SK *et al.* (2012):** Perinatal outcome in pregnancies with intra-uterine growth restriction by using umbilical and middle cerebral artery colour Doppler. J. Indian Med. Assoc., 110(3):154- 163.
23. **Borrelli AL, Zurzolo VS, Felicetti M *et al.* (2005):** The importance of Doppler ultrasonography in the management of fetal growth restriction. J. Obstet. Gynaecol.,60(4): 301–311.
24. **Wang KG, Chen CY and Chen YY (2009):** The effects of absent or reversed end-diastolic umbilical artery Doppler flow velocity. Taiwan J. Obstet. Gynecol., 48(3):225-31.
25. **Jang DG, Jo YS, Lee SJ *et al.* (2011):** Perinatal outcomes and maternal clinical characteristics in IUGR with absent or reversed end-diastolic flow velocity in the umbilical artery. Arch. Gynecol. Obstet., 284(1):73-8.
26. **Lakshmi C, Pramod G, Geeta K *et al.* (2013):** Outcome of Very Low Birth Weight Infants with Abnormal Antenatal Doppler Flow Patterns, A Prospective Cohort Study. Indian Pediatr., 5: 83-89.
27. **Cooley SM, Donnelly JC, Walsh T *et al.* (2011):** The impact of umbilical and uterine artery Doppler indices on antenatal course, labor and delivery in a low-risk primigravid population. J. Perinat. Med., 39(2):143-9
28. **Bolz N, Kalache KD, Proquitte H *et al.* (2013):** Value of Doppler sonography near term: can umbilical and uterine artery indices in low-risk pregnancies predict perinatal outcome? J. Perinat. Med., 41(2):165-70.
29. **Nanthakomon T, Uerpairojkit B (2010):** Outcome of small-for-gestational-age fetuses according to umbilical artery Doppler: is there any yield from additional middle cerebral artery Doppler? J. Matern. Fetal Neonatal Med., 23(8):900-5.
30. **Morales-Roselló J, Hervás-Marín D and Perales-Marín A (2013a):** Proximity of term labor deepens the fall of Doppler impedance in the fetal cerebral arteries. J. Matern. Fetal Neonatal Med., 18:15-36.
31. **Morris RK, Say R, Robson SC *et al.* (2012):** Systematic review and metaanalysis of middle cerebral artery Doppler to predict perinatal wellbeing. Eur. J. Obstet. Gynecol. Reprod. Biol., 165(2):141-55.
32. **Morales RJ, Hervás MD, Perales MA *et al.* (2013b):** Doppler study of the fetal vertebral and middle cerebral arteries in fetuses with normal and increased umbilical artery resistance indices. J. Clin. Ultrasound, 41(4):224-9.
33. **Babovic I, Plesinac S (2012):** Doppler examination in the evaluation of outcomes in pregnancies complicated by gestational hypertension and fetal intrauterine growth retardation--is it enough? Clin. Exp. Obstet. Gynecol., 39(2):222-4.