European Review for Medical and Pharmacological Sciences 2013; 17: 1599-1603

Predictive value of umbilical artery Doppler for adverse perinatal outcome in patients with HELLP syndrome

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Abstract. – OBJECTIVE: In this study, we aimed to evaluate in a prospective design the importance of pathologic umbilical artery (UA) Doppler findings as a predictive marker for neonatal outcome in patients with HELLP syndrome.

PATIENTS AND METHODS: A total of 45 pregnant women at 24-42 weeks of gestation with a diagnosis of HELLP syndrome were included. The study group consisted of 20 patients with abnormal UA Doppler results, and the remaining 25 HELLP syndrome patients with normal UA Doppler results were assigned to the control group. All patients were followed up until delivery, and the neonatal characteristics were compared.

RESULTS: Baseline characteristics of the groups were similar. In the study group, gestational week at delivery and infant birth weight were significantly lower ($p < 0.05$). The rates of significant neonatal morbidity, neonatal mortality, and neonatal intensive care unit (NICU) admission were significantly higher in study group patients ($p < 0.05$).

CONCLUSIONS: UA Doppler abnormalities can be considered predictive of poor neonatal prognosis in patients with HELLP syndrome, as they were significantly related with higher rates of neonatal mortality and significant morbidity.

Key Words:
Doppler ultrasonography, Blood flow velocity, HELLP syndrome, Perinatal mortality, Neonatal mortality.

Introduction

After the introduction of Doppler ultrasound to modern obstetric practice, noninvasive assessments of blood supply in fetal, placental, and maternal vessels became possible. In normal pregnancy, there is a reduction of the values of various Doppler indices in the umbilical artery (UA) due to the invasion of cytotrophoblasts into the spiral arteries leading to the loss of the muscular component as well as the dilatation and uncoiling of these uteroplacental vessels[1,2]. This results in the progressive loss of vascular impedance and an increase in end diastolic flow in the latter half of pregnancy[1,3]. Inadequate placental perfusion is associated with a rise in fetoplacental vascular resistance leading to a progressive decrease in the diastolic flow in the UA[4]. The most severe cases are characterized by absent end diastolic flow (AEDF) and by the appearance of reverse end-diastolic flow (RF) in the UA[3,5]. The association between pathologic UA Doppler findings and poor perinatal outcome is well known[4,5]. Fetuses with abnormal UA Doppler results are at a significantly increased risk for oligohydramnios, early delivery, decreased birth weight, and neonatal intensive care unit (NICU) admissions. The application of UA Doppler velocimetry in high-risk pregnancies has been associated with a trend of fewer perinatal deaths, labor inductions, and hospital admissions[5,6].

Ten percent of all pregnancies are complicated by hypertensive disorders. HELLP syndrome was first defined by Weinstein[7] in 1982 as a combination of hemolysis (H), elevated liver functions (EL), and low platelet count (LP), and this constellation occurs in almost 20 percent of women with severe preeclampsia. A relationship exists between the occurrence of HELLP syndrome and increased maternal and perinatal mortality and morbidity. Thus, in the presence of these findings, it is generally recommended to expedite the delivery. It was generally believed that infant outcomes in patients with HELLP syndrome were primarily related to gestational age at delivery rather than the hypertensive disorder per se[8,9].

The etiology and pathogenesis of hypertensive disorders of pregnancy, including preeclampsia and HELLP syndrome, remain unknown, but abnormal development of placental

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vasculature is considered the main pathophysiological mechanism [1,2]. Regarding malplacentation as the main pathological event in preeclampsia and HELLP syndrome, alteration in UA Doppler velocimetry is expected. The present study aimed to compare the neonatal outcomes of HELLP syndrome patients, with or without abnormal UA Doppler values, in order to determine the potential role of abnormal UA Doppler findings as a predictor of worse neonatal outcome.

Patients and Methods

This prospective clinical trial was conducted in the High-risk Pregnancy Unit of Dr. Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey, between January 2008 and December 2009. The study was conducted in accordance with the basic principles of the Declaration of Helsinki. It was approved by the Ethics Committee of the Institute. All study participants were fully informed of the aim of the study and provided informed consent.

A total of 45 pregnant women with a diagnosis of HELLP syndrome at 24-42 gestational weeks were included in the study.

HELLP syndrome was defined as the presence of the following laboratory investigations in preeclamptic pregnant women: serum lactate dehydrogenase (LDH) level > 600 IU/L, aspartate aminotransferase level > 70 IU/L, and platelets count[7,9] < 100.000/mm^3.

The pregnancies were dated by a combination of last menstrual period and first-trimester-dating scan. Detailed ultrasound scans were performed on all fetuses. Patients with diabetes mellitus, chronic hypertension, hepatic diseases, renal diseases, a thromboembolic event or known thrombophilic disorders, multifetal gestation, or fetuses with chromosomal or structural abnormalities were excluded.

All women included in the study were subjected to UA Doppler measurements in addition to fetal weight assessments, estimated according to the Hadlock et al formula[10]. Measurements were made with a 3.5 mHz pulsed vector transducer using a color Doppler ultrasound with a high-pass filter set at 100 Hz. While the patient was lying in a semi-recumbent position in order to prevent aortocaval pressure, the UA was identified, and flow velocity waveforms were obtained from a free-floating segment away from the placental and fetal insertion sites. Recordings were accepted for analysis only after a clear steady state was obtained for a minimum of three to five consecutive pulsatile arterial waveforms. All sonographic recordings were performed by the same expert sonographer. For the purpose of analysis, the study population was distributed in two groups: a normal UA Doppler group and an abnormal Doppler group.

Patients with diminished flow (DF), AEDF, and RF in UA were recruited for the study group. DF was determined as the ratio of peak-systolic to end-diastolic blood flow velocities (S/D) being equal or greater than the 95th percentile[11].

After stabilization of the maternal clinical condition and corticosteroid (CS) treatment, all patients received labor induction with no extra considerations.

The main outcome measures were significant neonatal morbidity and mortality, NICU admissions, Apgar scores, and birth weight measurements. Significant neonatal morbidity was defined as the presence of any one of the following: respiratory distress syndrome (RDS), necrotizing enterocolitis (NEK), intraventricular hemorrhage (IVH) or periventricular hemorrhage (PVH), sepsis, pneumonia, retinopathy of prematurity (ROP).

Statistical Analysis

Results obtained were expressed as means ± SD, and statistical analyses were performed by Chi-square, independent *t*-test, ANOVA test, and logistic regression utilizing SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA) with $p < 0.05$ being considered statistically significant.

Results

Forty-five pregnant women met the inclusion criteria over the study period. There were 20 patients in the study group and 25 patients in the control group. Obstetric characteristics of the study and control groups are shown in Table I. Maternal age, parity, previous healthy children, and severity of HELLP syndrome (based on blood pressure and platelets count) were similar between the groups. In the study group, gestational week at delivery and infant birth weight were significantly lower ($p < 0.05$).

Table I. Demographic data of both groups.

Variables	Control group, n = 25	Study group, n = 20	p value
Age	25.3 (18-36)	29.9 (19-40)	0.260
Gravidity	1.8 (1-3)	2.8 (1-5)	0.458
Parity	1 (0-2)	1 (0-4)	0.637
Previous healthy children	1 (0-2)	1 (0-3)	0.631
Systolic blood pressure (mmHg)	158 ± 11.98	158 ± 14.76	0.832
Diastolic blood pressure (mmHg)	102.8 ± 6.29	105 ± 7.77	0.437
Platelets count	100.000 ± 19.380/mm^3	97.000 ± 22.000/mm^3	
Gestational week at delivery	33.7 ± 2.7	31.5 ± 3.7	0.037
Cesarean delivery	12 (48%)	13 (65%)	0.254
Birth weight (g)	1919 ± 683	1375 ± 828	0.019

The mean S/D ratio in the control group was 2.44 (2-2.80). The distribution of pathologic UA Doppler findings in the study group is shown in Table II.

Neonatal outcomes of the groups are presented in Table III. The rates of significant neonatal morbidity, neonatal mortality, and NICU admission were significantly higher in patients in the abnormal UA Doppler group ($p < 0.05$).

Discussion

The reported maternal mortality rate of HELLP syndrome ranges from 0 to 24%, and the perinatal mortality rate ranges from 8 to 40%[12,14]. The main aim of the protocols for the management of HELLP syndrome is first to reduce maternal mortality and morbidity rates and second to deliver a healthy baby[15]. In our study, neonatal mortality rates were 15% in the control group and 40% in the study group, respectively, and comparable with the relevant literature[12,14]. It was believed that increased perinatal mortality rates were mainly due to stillbirths, and neonatal mortality appears to be primarily related to the gestational age at delivery in patients with HELLP syndrome[9,14-17]. However, it is well known that HELLP syndrome is a variant presentation of severe preeclampsia[9]. The exact etiology of preeclampsia is unknown, but disordered placental implantation with abnormal trophoblastic invasion of uterine vessels plays a major pathophysiologic role in the development of preeclampsia[1,2,9]. Regarding uteroplacental abnormality as the main pathological event in cases of pregnancy-specific hypertensive disorders, alteration in UA Doppler velocimetry could be expected. Various studies have shown that in pregnancies accompanied by uteroplacental insufficiency, UA Doppler velocimetry can discriminate those at high risk for adverse neonatal outcome. Baschat et al[18] and Soregaroli et al[19] have reported that small for gestational age (SGA) fetuses with normal UA Doppler indices do not

Table II. Distribution of pathologic findings in UA Doppler of study group.

UA Doppler outcome	N (%)
Diminished Flow	6 (30)
AEDF	12 (60)
RF	2 (10)

Table III. Comparison of neonatal outcomes of both groups.

Variables	Control group, n = 20	Study group, n = 25	p value
Apgar score < 7 at 5 minutes	9 (45%)	9 (36%)	0.665
Significant neonatal morbidity	16 (80%)	11 (44%)	0.014
NICU admission	18 (90%)	11(44%)	0.001
Neonatal mortality	8 (40%)	3 (15%)	0.03

show increased morbidity compared to pregnancies with SGA and intrauterine growth restricted (IUGR) fetuses presenting with increased S/D ratio, AEDF, and RF in UA Doppler. Similarly, in their prospective study, Seyam et al[20] also demonstrated that pregnancies with normal UA Doppler blood flow are associated with decreased risk for oligohydramnios (31.3% vs. 60.2%, $p = 0.037$), neonatal birth weight of less than tenth percentile (37.5% vs. 73.8%, $p = 0.004$), and NICU admissions (0% vs. 26.5%, $p = 0.02$) compared to pregnancies with abnormal Doppler blood flows. In a recent study, Spinillo et al[21] reported that in pregnancies accompanied by IUGR, AEDF and RF in UA Doppler are independent predictors of increased risk of either neonatal death or cerebral palsy.

In the present investigation, we observed that abnormal UA Doppler values in pregnancies with HELLP syndrome are associated with increased incidence of adverse neonatal outcome (neonatal mortality and morbidity rates were 40% and 80%, respectively). Morbidity was significantly increased in IVH, sepsis, and mechanical ventilation treatment rate in the abnormal Doppler group compared to patients with HELLP syndrome and normal UA Doppler findings (90% and 44%, respectively). Furthermore, mean birth weight and mean gestational age at delivery were significantly lower in the study group.

According to our current knowledge, UA Doppler analysis as a risk factor for poor neonatal outcome in cases of HELLP has not been previously studied. We demonstrated for the first time that abnormal UA Doppler results predicted worse neonatal outcomes in this selected group of high-risk patients, irrespective of gestational age.

Management and delivery of HELLP syndrome mothers and infants should be performed at tertiary centers where highly trained NICU personnel and facilities are available[15]. Doppler studies of UA in these cases can provide important information to the obstetrician and pediatrician and improve outcome for neonates born to mothers with HELLP syndrome. Our data indicates that UA velocimetry can distinguish those fetuses at risk of neonatal complications.

Conclusions

DF, AEDF, and RF in UA Doppler are independent prognostic factors for neonatal outcome in patients with HELLP syndrome. These findings seem to be related with significantly increased neonatal morbidity and mortality rates. Although no method currently exists to prevent the development of hypertensive diseases of pregnancy and HELLP syndrome, UA Doppler velocimetry can be used as a valuable tool to assist clinicians in predicting neonatal outcome. Umbilical flow velocimetry studies should be an integral parameter when evaluating patients with HELLP syndrome.

Conflict of Interest

None to declare.

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