Color Doppler Evaluation of Cerebral-Umbilical Pulsatility Indices and Ratio and Its Usefulness at High Risk Pregnancy

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Abstract:

Objective: The correlation between cerebro-umbilical pulsatility indices and high risk pregnancy. Subjects: The study was included 40patients, 20 preeclampsia patients, 20 gestational diabetes patients. **Methods:** All patients in the study underwent ultrasound assessment that includes fetal biometry, fetal weight, a four component biophysical profile score and Doppler ultrasound studies of umbilical artery (UA) and middle cerebral artery (MCA). **Results:** The study was included 40 patients with high risk pregnancy. They were classified into 2 groups according to the risk pre-eclampsia group and diabetic group whether the two groups are equal in number being 20 per each.UA-PI is significant higher in pre-eclampsia group than diabetic group as well as MCA-PI and C/U ratio is significantly lower in pre-eclampsia group than diabetic group. **Conclusion:** Doppler investigation of the cerebro – umbilical pulsatility indices and ratio play an important role in monitoring high risk pregnancies complicated by placental vascular insufficiency and fetal growth restriction (FGR). In a relatively well controlled diabetic pregnancies not complicated by preeclampsia or FGR the values of color Doppler indices are similar to normal pregnancy

Keywords: Doppler indices, High risk pregnancy.

Introduction:

A high risk pregnancy is one in which some condition puts the mother, the developing fetus, or both at higher-than-normal risk for complications during or after the pregnancy and birth. A pregnancy can be considered a high-risk pregnancy for a variety of reasons such as: maternal age, women who will be under age 17 or over age 35, medical conditions specific to pregnancy, such as fetal growth restriction, antepartum haemorrhage, multiple pregnancy and prolonged pregnancy.

Medical conditions that exist before pregnancy : Such as diabetes, hypertensive disorders (chronic hypertension and pre-eclampsia), cardiac, renal and autoimmune disorders **(1).** More recently, thrombophilias (congenital and acquired) have been added to this list **(2).**

Doppler ultrasound is a well-established technique used to diagnose problems during pregnancy. Doppler ultrasound can monitor how fast blood is moving in the umbilical blood flow**.**

The waveforms were derived from the changes in the ultrasound frequency of the Doppler signal, which targeted circulating fetal blood within umbilical artery. Such flow velocity waveforms (FVW) from the feto-placental circulation are dependent on the fetal cardiac contraction force, density of the blood, the vessel wall elasticity and peripheral or downstream resistance **.**It was suggested that the FVWs should be obtained with the mother in a semi–recumbent position during a period of fetal inactivity, as the impedance indices are moderated by fetal breathing and elevated fetal heart rates.

Doppler ultrasound in high-risk pregnancies appears to reduce the number of babies who die, and may also lead to fewer obstetric interventions. However, the evidence was of moderate Doppler Exam Improves Outcomes in High-Risk Pregnancy

Using Doppler ultrasound to examine fetal circulation, reduces perinatal death in high-risk pregnancies by 29% as an updated Cochrane Review found.

SUBJECTS AND METHODS:

The study was designed as an observational cross sectional study, 40 pregnant women attending to radiological department at Benha Teaching Hospital in the period from June 2018 to Mars 2019. The sample size was divided into 20 pregnant women diagnosed as preeclampsia and 20 pregnant women diagnosed as gestational diabetes. Written consents were taken from patients. The research was approved by ethical committee of the Benha Teaching Hospital.

Inclusion criteria were:

1. Singleton pregnancy.
2. Gestational age between 30 – 36 weeks.
3. Preeclampsia (mild & severe) defined as presence of hypertension (BP ≥140/90 mm Hg) on 2 occasions, at least 6 hours apart in a woman who was normotensive before 20 weeks' gestation and proteinuria > 0.3gm/24 hours or > 1 + dipstick
4. Gestational diabetes mellitus defined as any degree of glucose intolerance first recognized during pregnancy. A fasting

plasma glucose level >126 mg/dl or a random plasma glucose >200 mg/dl.

Exclusion criteria were:

1. Multiple pregnancies.
2. Multiple pathologies (more than one disease)
3. Fetuses with congenital anomalies.

Technique of scanning: All patients in the study underwent ultrasound assessment that includes fetal biometry, fetal weight, a four component biophysical profile score and Doppler ultrasound studies of umbilical artery (UA) and middle cerebral artery (MCA).

Ultrasound equipments capable of high resolution gray-scale, pulsed wave and color Doppler modes were used (Logic 5, Logic 7, Toshiba) with a convex transducer 3.5 MHZ.

Conventional 2D ultrasound fetal biometry was performed as follows:

Scanning for Biparietal Diameter and head Circumference: The BPD was measured in the scan which shows the widest diameter at the level of midline echo complex (the inter - hemispheric fissure), two lateral ventricles and the thalami. The reference point for BPD is the measurement from the inner margin of distal skull interface to outer margin of proximal skull interface. Head circumference was measured in the same plane used for BPD measurement.

Scanning for Abdominal Circumference: The transducer was then placed at right angle to the plane between the heart and the bladder. This assured that the level of the point at which the abdominal circumference was perfectly circular and included the liver, the horizontal portion of the portal vein, as well as the stomach bubble and the fetal spine. The abdominal circumference was measured using the electronic calipers with maximum diameters using outer to outer technique.

Scanning of Femur Length: Once the femur was located, an attempt was made to define both the ends of the calcified portion of the femur. This is done most accurately if both the soft tissues of the buttock and the knee joint can be seen and which usually avoids tangential section of the bone.

Estimated fetal weight (EFW): is calculated automatically**.**

Scanning for amniotic fluid index: Amniotic fluid volume was estimated by measuring the deepest vertical pocket of liquor amnii which was free of any fetal part or umbilical cord. A measurement of < 2cm was considered as oligohydramnios, 2–8 cm as normal amniotic fluid volume and >8 cm as polyhydramnios. AFI of 5cm or less was

considered abnormal (oligohydramnios), while AFI more than 5cm till 24 cm was defined as normal, while AFI more than 24 cm was considered (polyhydramnios).

Doppler Examination:

Umblical artery: The umbilical artery flow spectrum was recorded from a free floating central part of the umbilical cord, an absent or reversed end-diastolic flow velocity is noted.

Middle cerebral artery: A transverse view of the fetal brain is obtained at the level of the biparietal diameter. The transducer is then moved towards the base of the skull at the level of the lesser wing of the sphenoid bone. Using color flow imaging, the middle cerebral artery can be seen as a major lateral branch of the circle of Willis, running anterolaterally.

Middle cerebral artery/Umbilical artery resistive index ratio (C/U ratio): It the ratio of resistive indices of fetal middle cerebral artery and umbilical artery .The cerebroplacental ratio (CPR) has been constructed using various Doppler indices (systolic/diastolic ratio, resistance index and pulsatility index) and cut-offs (< 1, < 1.05 and< 1.08) respectively to predict adverse outcome **(3)**. Pulsed wave Doppler measurements of UA, MCA were obtained using the pulsatility index (PI) to quantify arterial Doppler waveforms.

Biophysical profile scanning: A full four component BPP scoring was performed. Fetal breathing movement sustained for 30 seconds or more, presence of at least three body/limb movements, presence of at least one vigorous flexion/extension episode of the limbs and amniotic Fluid Index (AFI) above 5 cm. Two points were given for any components if these criteria were met. No points were given for any component if these cut-offs were not met in a 30 minutes period.

Outcome variables: Biophysical profile scores of 0, 2, 4 and 6 with oligohydramnios were defined as abnormal. Scores of 10, 8 and 6 without oligohydramnios were considered normal.

Statistical analysis The study group with high risk pregnancy were classified into 2 groups according to the cause (preeclampsia and diabetes). Out-come measures coded, entered and analyzed using Microsoft excel software. Data then were inserted into Statistical package for social science software (SPSS version 20) for statistical analysis.

According to the type of data; qualitative as number and percentage, quantitative data represented by mean ± SD. The following

tests were used to test difference for significance; t-test (t) for quantitative independent data, Chi square test (X^2) for difference and association of qualitative data.

P. value was set at **<0.05** for significant result &**<0.001** for highly significant results. Cut off values that could be differentiate between pre-eclampsia and diabetic groups are generated using ROC curve.

RESULTS:

The study was included 40 patients with high risk pregnancy. They were classified into 2 groups according to the risk pre-eclampsia group and diabetic group whether the two groups are equal in number being 20 per each.

Table 1: Distribution of age among the two groups

Age (yrs)	Groups		t-test	P	S
	Pre-eclampsia (N:20)	Diabetic (N:20)			
(mean ± SD)	31.15 ±2.64	30.8 ±3.16	0.38	0.7	NS

No significant difference between groups as regard means age.

Table 2: Distribution of GA and EFW among the two groups

Age (yrs)	Groups		t-test	P	S
	Pre-eclampsia (N:20)	Diabetic (N:20)			
G.A. (mean ± SD)	32.45 ± 1.67	32.55 ± 1.19	0.218	0.8	NS
EFW (mean ± SD)	1702.9 ± 298.7	1880 ± 438.9	1.5	0.1	NS

No significant difference between groups as regard means G.A. and EFW.

Table 3: Distribution of parity among the two groups:

			Groups		X^2	P	S
			Pre-eclampsia (N:20)	Diabetic (N:20)			
Parity	Nuli-para	N	12	4	6.66	0.01*	S
		%	60%	20%			
	Multi-para	N	8	16			
		%	40%	80%			
Total		N	20	20			
		%	100%	100%			

Significant association between nuli-para and pre-eclampsia group and multi-para and diabetic group.

Table 4: Distribution of Amniotic fluid and BPP among the two groups

			Groups Pre-eclampsia (N:20)	Diabetic (N:20)	X^2	P	S
Amniotic fluid	**Oligohydraminos**	**N**	**6**	**0**	**11.034**	**0.004***	**S**
		%	**30%**	**0%**			
	Polyhydraminos	**N**	**0**	**5**			
		%	**0%**	**25%**			
	Normal	**N**	**14**	**15**			
		%	**70%**	**75%**			
Total		**N**	**20**	**20**			
		%	**100%**	**100%**			
BPP	**Low score**	**N**	**6**	**0**	**7.059**	**0.008***	**S**
		%	**30%**	**0%**			
	Normal	**N**	**14**	**20**			
		%	**70%**	**100%**			
Total		**N**	**20**	**20**			
		%	**100%**	**100%**			

Oligohydraminos is significantly associated with Pre-eclampsia-group, while Polyhydraminos is significantly associated with diabetic group. As regard BPP; low score is significant associated with pre-eclampsia group.

Table 5: Distribution of different Doppler indices among the two groups

	Groups Pre-eclampsia (mean ± SD)	Diabetic (mean ± SD)	t-test	P	S
UA-PI	**1.79 ± 0.58**	**1.36 ± 0.49**	**2.505**	**0.01***	**S**
MCA-PI	**1.29 ± 0.34**	**1.58 ± 0.46**	**2.266**	**0.02***	**S**
C/U ratio	**0.87 ± 0.55**	**1.39 ± 0.74**	**2.499**	**0.01***	**S**

UA-PI is significant higher in pre-eclampsia group than diabetic group as well as MCA-PI and C/U ratio is significantly lower in pre-eclampsia group than diabetic group.

Table 6: Difference between two groups regarding Doppler ultrasound findings of the umbilical artery end diastolic flow.

			Groups Pre-eclampsia (N:20)	Diabetic (N:20)	X^2	P	S
UA EDF	**Absent**	**N**	**8**	**4**	**1.905**	**0.1**	**NS**
		%	**40%**	**20%**			
	Present	**N**	**12**	**16**			
		%	**60%**	**80%**			
Total		**N**	**20**	**20**			
		%	**100%**	**100%**			

No significant difference among the two groups as regard UA EDF

Table 7: validity of association between each of umbilical artery PI, middle cerebral artery PI , C/U ratio and (pre eclampsia , gestational diabetes).

	AUC	P	Cut-off value	Sensitivity	Specificity	PPV	NPV
UA PI	**0.72**	**0.01***	**>1.28**	**80%**	**55%**	**64%**	**73.3%**
MCA PI	**0.7**	**0.02***	**<1.37**	**70%**	**55%**	**60%**	**64%**
C/U ratio	**0.73**	**0.01***	**<1.39**	**80%**	**55%**	**64%**	**73.3%**

Significant association between pre-eclampsia and Doppler indices (UA PI, MCA PI and C/U ratio). UA PI show (area under curve (AUC) = 0.72 & P=0.01) and at cut off value >1.28 could be differentiate pre-eclampsia from diabetic group with sensitivity 80%, specificity 55%, Positive predictive value (PPV) 64% and negative predictive value (NPV) 73.3%. MCA PI show (AUC =0.7 & P=0.02) and at cut off value <1.37 could be differentiate pre-eclampsia from diabetic group with sensitivity 70%, specificity 55%, (PPV) 60% and (NPV) 64%. C/U ratio show (AUC =0.73 & P=0.01) and at cut off value <1.39 could be differentiate pre-eclampsia from diabetic group with sensitivity 80%, specificity 55%, (PPV) 64% and (NPV) 73.3%

CASE PRESENTATION

Pregnant female 35 years old, with history of gestational diabetes coming for antenatal care, GA by LMP =33weeks 2days, GA by U/S =34 weeks 1day, EFW =2704gm > 50th percentile and BPP score =8 (normal).

Doppler examination of the fetus revealed, normal umbilical artery Doppler and normal middle cerebral artery Doppler.

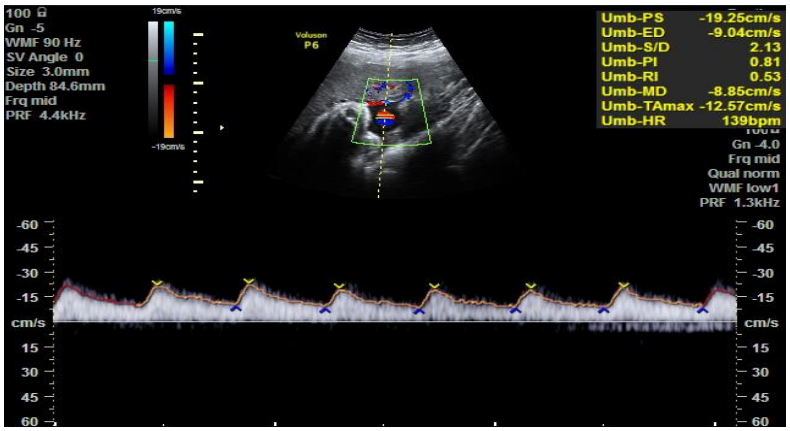

Fig.1: Case 1, UA Doppler showing normal waveform and Doppler indices (RI=0.53, PI=0.81).

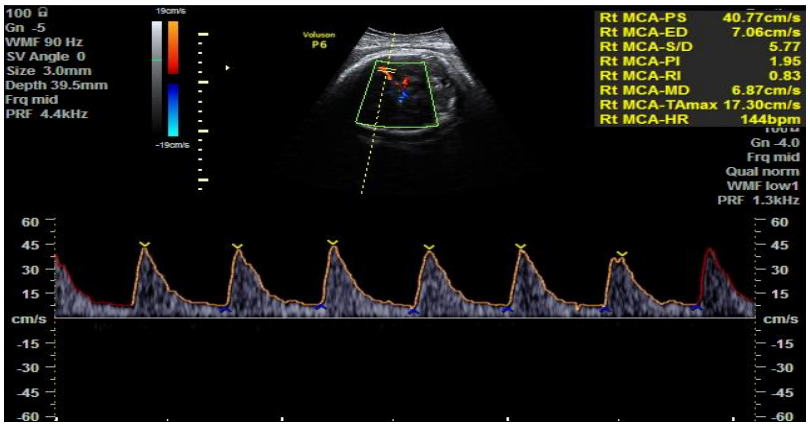

Fig.2: Case 1, MCA Doppler showing normal waveform and Doppler indices (RI=0.83, PI=1.95).

Discussion:

Different methods for the assessment of fetal wellbeing have been proposed for monitoring of high-risk pregnancies: fetal cardiotocography , biophysical profile, Doppler evaluation of the fetal circulation (arterial and venous) and Doppler evaluation of maternal circulation (uterine artery)**.**

Doppler ultrasound study of utero-placental blood vessels, using waveform indices or notching, may help to identify the 'at-risk' women, such that interventions might be used to reduce maternal and fetal morbidity and/or mortality **(4).**

Interventions, like early delivery, might then be able to reduce the mortality and morbidity. However, it may also be that the use of Doppler ultrasound could increase the use of caesarean section.

The aim of the study to assess the use of Doppler ultrasound in high risk pregnancies and investigate flow velocity waveforms in the umbilical artery, middle cerebral artery improving subsequent obstetric care and fetal outcome.

A total of 40 pregnant women were included in this study, 20 of them were preeclampsia patients and 20 were gestational diabetes patients. All pregnant women underwent uniform antenatal assessment protocol that includes a four component biophysical profile score, umbilical artery (UA) and middle cerebral artery (MCA) ultrasound studies.

Mothers in the age group of (25-35 years) mean age (31.15±2.64) years, comprised the preeclampsia group. While gestational diabetes group had age ranging from (26- 35 years) mean age (30.8±3.16) years.so according to results no significant difference between groups as regard to age.

In the preeclampsia group, most of the patients were primipara (60%).While at

gestational diabetes group most of the patients were multipara (80%). Otherwise; distribution of parity shows that primipara in whom age ranges from (25–35 years) are at risk for preeclampsia and multipara whom age ranges from (26-35) are at risk for gestational diabetes. In our study gestational age at the time of examination was (30–34weeks) mean (32.45±1.67) weeks in the preeclampsia groups, while at gestational diabetes groups gestational age at the time of examination was (32-39 weeks) mean (32.55±1.19).

In this study, both BPP and AFI predictors were significant at preeclampsia , out of 20 case of preeclampsia 6 cases had abnormal BPP scoring and 6 cases had oligohydraminous, while out of 20 cases of gestational diabetes no case had abnormal BPP and 5 cases had poly hydraminous.

Doppler ultrasonography and biophysical profile scoring (BPS) are the principal surveillance tools in pregnancies complicated by placental vascular insufficiency and fetal growth restriction (FGR) **(5).**

It was reported in prediction of perinatal outcome in high risk women at or above 34 weeks gestation; that Doppler velocimetry had more sensitivity, specificity and negative predictive values than Biophysical profile **(6).**

In accordance with study that demonstrated pregnancies with normal umbilical artery Doppler blood flow are associated with decreased risk for oligohydramnios compared to pregnancies with abnormal Doppler blood flows.

The mean EFW in preeclampsia group was lower as compared to the normal range. By this we can say that preeclampsia has major effects on the growth of the fetus.

The mean EFW in gestational diabetes group was higher as compared to the normal range. It was stated before that uncontrolled maternal hyperglycemia adversely influences fetal weight and growth with resultant macrosomia at moderately elevated levels and intrauterine growth restriction at very high levels of maternal blood glucose **(7)**.

Doppler indices at preeclampsia group comparing to gestational diabetes group:

UA-PI is significant higher in pre-eclampsia group than diabetic group as well as MCA-PI and C/U ratio is significantly lower in pre-eclampsia group than diabetic group.

Umbilical artery Doppler velocity waveform

The umbilical artery has been the first and the most studied artery since the

introduction of Doppler ultrasound in obstetrics. The absence of diastolic flow or reversed diastolic blood is often associated with adverse outcome of pregnancy, e.g. IUGR and fetal hypoxia **(8).**

The mean umbilical artery PI were higher at preeclampsia group (1.79±0.58) mean than diabetic group (1.36±0.49) mean. In our study out of 20 patients who had preeclampsia 14 patients had abnormal umbilical artery Doppler indices (70%), among them 6 patients had reduced end diastolic flow and 8 patients had absent end diastolic flow, no case of reversal end diastolic flow in umbilical artery was noted.

In our study out of 20 patients who had diabetes 10 patients had abnormal umbilical artery Doppler indices (50%), among them 6 patients had reduced end diastolic flow and 4 patients had absent end diastolic flow , no case of reversal end diastolic flow in umbilical artery was noted.

Some researchers showed in their study in the high-risk group with abnormal umbilical artery Doppler indices (60 cases), that 31 cases had reduced end diastolic flow, while absent end diastolic flow was present in 13 cases and 2 cases had reversed end diastolic flow **(9).**

They also stated that the umbilical artery Doppler is valuable in investigation of high risk pregnancy although it is not a good screening tool in the low risk population. Perinatal morbidity and mortality is higher in high risk group with abnormal umbilical artery Doppler flow (9).

It was stated that unlike in the IUGR model, the pathophysiological basis for the increase in placental vascular resistance in diabetic pregnancy is functional rather than structural and is attributed to hyperglycemia (9). Hyperglycemia is thought to cause an increase in the thromboxane/prostacyclin ratio in the umbilical vessels and the placenta. Another contributing factor is fetal polycythemia. As a result, we have to interpret the Doppler results of the UA and MCA with caution in the management of GDM pregnancies as normal Doppler findings may give false reassurance on the pregnancy outcome.

Comprising of 16 studies and involving 10, 225 babies showed that fetal and umbilical artery Doppler ultrasound in high risk pregnancies can decrease the perinatal mortality by 29 % when obstetric services were in place to ensure safe and timely delivery of the baby when needed.

However the presence of normal umbilical artery Doppler does not rule out the chance of perinatal morbidity as the changes in the Doppler indices do not occur in mild forms

of placental insufficiency and they become abnormal only in advanced stages of placental dysfunction

Researchers found no significant changes in the fetal circulation in Doppler study of a relatively well-controlled diabetic pregnancies except when complicated by preeclampsia or severe FGR **(10)**.

Middle cerebral artery Doppler velocity waveform

Fetal MCA is a low resistance circulation throughout pregnancy. If there is continued and progressive fetal hypoxia, a phenomenon known as "brain sparing effect" is seen with dilation of the fetal intracranial vessels, which provides increased blood flow to the brain at the expense of other organs. The Doppler waveform depicts this as increase in diastolic flow with decreased pulsatility index (**11**).

The mean MCA artery PI is lower in preeclampsia group (1.29±0.34) (mean±SD) compared to diabetes group (1.5 8±0. 64) (mean±SD). In our study, out of 20 patients who had preeclampsia 10 (50%) patients had abnormal middle cerebral artery Doppler indices. In our study, out of 20 patients who had diabetes 4(20%) patients had abnormal middle cerebral artery Doppler indices.

It was noted that the mean MCA PI at 34 weeks was 1.51 in the high risk group and 1.74 in the control group. In their longitudinal analysis of fetal circulation, it was shown that the MCA indices were different in the high risk group than the normal group (9).

Though MCA indices are not useful parameters for identification of fetuses at risk, abnormal MCA PI values were highly suggestive of poor perinatal outcomes in fetuses with abnormal uterine and umbilical velocimetry **(12).** It was also shown that gestational diabetes may contribute to an elevated PI in the fetal MCA. Although there is not yet strong proof for the effect of GDM on the fetal brain hemodynamics, the significant higher MCA PI warrants more attention towards better controlling of the hyperglycemia during pregnancy (12).

It was concluded that a normal MCA PI is helpful to identify the fetuses without a major adverse perinatal outcome, hence once the umbilical artery PI is abnormal, it is better to perform the MCA PI to know the extent of brain sparing stressing the importance of studying two vessels in the Doppler.

It was shown that gestational diabetes may contribute to an elevated PI in the fetal MCA. Although there is not yet strong proof

for the effect of GDM on the fetal brain hemodynamics, the significant higher MCA PI warrants more attention towards better controlling of the hyperglycemia during pregnancy

In a previous research, no significant changes were found in the fetal circulation in Doppler study of a relatively well-controlled diabetic pregnancies except when complicated by preeclampsia or severe FGR (10)

Middle cerebral artery/Umbilical artery resistive index ratio (C/U ratio)

Recently, the cerebral /umbilical ratio(C/U ratio) has been recognized as the more sensitive and specific indicator of likelihood of IUGR and adverse perinatal outcome in high-risk pregnancies. The cerebroplacental ratio (CPR) has been constructed using various Doppler indices (systolic/diastolic ratio, resistance index and pulsatility index) and cut-offs (< 1, < 1.05 and< 1.08) respectively to predict adverse outcome (**13)**.

(11) calculated in their study that included 90 patients the cerebro-umbilical ratio (C/U) (the ratio of MCA PI to umbilical artery PI) and found that it remained constant in the last 10 weeks of pregnancy and therefore used a single cut off value of 1.08 for all cases of 31-40 weeks of gestation. Above this value, Doppler velocimetry were considered normal and below it abnormal.

In the present study, we found that out of 20 patients of preeclampsia group, abnormal C/U ratio was seen in 14 cases (70%) ,we found that out of 20 patients of diabetes group, abnormal C/U ratio was seen in 12 cases (60%).

The reliability of C/U ratio in the estimation of fetal condition in preeclamptic patients was proved to be high. Very low C/U ratio values in patients with preeclampsia indicate that in these fetuses, fetal acidosis and fetal distress may be expected.

Conclusion:

Doppler investigation of the cerebro – umbilical pulsatility indices and ratio play an important role in monitoring high risk pregnancies complicated by placental vascular insufficiency and fetal growth restriction (FGR).

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