Original Article

Correlation Between Umblical Artery Doppler Indices With Neonatal Cord Blood Ischemic Modified Albumin in Diagnosis of Neonatal Asphyxia in High Risk Pregnancy

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ABSTRACT

Background: Neonatal asphyxia is a significant cause of neonatall morbidity and mortality worldwide.

Aim: This study aims to is to evaluate the significance of the cord blood ischemia-modified albumin (IMA) level as a diagnostic marker for neonatal asphyxia and to determine the associations of IMA levels with doppler findings in diagnosis of neonatal asphyxia in high risk pregnancy.

Materials and Methods: This is a prospective case control study that will be performed at obstetrics and gynecology department at Al-zahraa University Hospital. The study was carried out on 90 pregnant women who are attend the obstetrics department for labour and divided into two groups: Group A:(control group)it was include 30 healthy pregnant women. Group B:(study group) it was include 60 pregnant women with high risk pregnancy. Doppler measurements were obtained from umbilical and middle cerebral arteries,C/P ratio.IMA was measured by ELISA kits and expressed as picomole per milliliter.

Results: Ischemia-modified albumin levels were significantly higher in neonates of complicated pregnancies as compared to uncomplicated pregnancies *(P<0.001*). They were higher in newborns with neonatal asphyxia as compared to healthy controls (*P=0.004*).The C/P ratio-pulsatility index (PI) showed a significant difference between normal and complicated pregnancies with neonatal asphyxia (*P<0.0001*). IMA levels were significantly increased in cases with abnormal C/P ratio-PI.

Conclusion: Cord blood IMA levels may be accepted as a useful marker in diagnosis of neonatal asphyxia in high risk pregnancy. Abnormal umblical artery Doppler examinations are associated with elevated IMA levels in high risk pregnancy.

Key Words: Doppler study, high risk pregnancy, ischemia-modified albumin, neonatal asphyxia

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INTRODUCTION

Neonatal Asphyxia is a term that generates anxiety for most birth attendants. Not only does it contribute to a large number of neonatal deaths and long-term disabilities in children worldwide, but it can have a long lasting impact on the careers of the obstetricians and midwives concerned. Obstetric claims related to mishaps during labour, leading to neonatal asphyxia and long-term neurological damage to the newborn, are associated with enormous costs of financial compensation for families who have to suffer the emotional distress and care for a possibly life-long handicapped child[3]. An insufficient supply of oxygen before, during or just after delivery was assumed to be the cause. Therefore, different tests have been investigated for the prediction of fetuses at risk for hypoxic brain damage and hopefully to prevent this damage, but many of them have remained limited[7].

In recent clinical studies, it has been found that ischemia-modified albumin (IMA) is a new biochemical marker for the early diagnosis of myocardial ischemic events and cerebrovascular accidents. IMA is a modification of human serum albumin (HSA). N-terminal amino acids of HSA temporarily bind to transitional metals such as cobalt, nickel and copper. Hypoxia,acidosis or ischemia leads to achange on this region and reduce the binding capacity of HAS to these metals. The resulting molecule is called IMA. IMA rapidly increases within 5 to 10 min after the ischemic event and remains high for 30 min. It returns to baseline 12 h after the ischemia event, but if the ischemic event persists, it continues to rise[4]. Doppler ultrasound imaging is presently used for management and follow-up in pregnancies complicated with avariety of common diseases such as hypertension and diabetes mellitus, in which blood flow through the placenta is compromised. In response to hypoxia resulting from placental insufficiency, fetal compensatory mechanisms redistribute blood flow toward essential fetal organs. The early stage of this redistribution results in increased blood flow to the brain and is detected with increased resistance of the umbilical artery (UA) and decreased resistance of the middle cerebral artery(MCA)

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at Doppler examination. The cerebral/placental ratio (C/P ratio) becomes less than one. It has been called the 'brain sparing effect' and it has been suggested that the C/P ratio alone was amore precise index than others[10]. In these considerations, the primary aim of this study was to evaluate the significance of the cord blood ischemia-modified albumin (IMA) level as a diagnostic marker for neonatal asphyxia and to determine the associations of IMA levels with doppler findings in diagnosis of neonatal asphyxia in high risk pregnancy.

PATIENTS AND METHODS

This prospective, case-control study was performed between March 2019 to October2019,and was approved by the local research ethics committee. All mothers included in the study provided signed, informed consent before recruitment. A total of 90 pregnant women were included in the study. Thirty of them were with normal pregnancies and sixty with pregnancies complicated by pre-eclampsia, gestational diabetes mellitus (GDM) and/or intrauterine growth restriction (IUGR). seventeen newborns of these 90 patients were diagnosed as exposed to neonatal asphyxia. The Doppler examination was performed only after 33weeks' gestation There fore,this study was performed in pregnancies between 33 and 41 weeks' gestation. Fetal biometry was measured and weight calculated by the Hadlock formula. All Doppler examinations and ultrasound measurements were performed, Doppler measurements of UAandMC A were obtained Then the systolic–diastolic ratio (S/D), pulsatility index and resistance index were calculated for each artery. The C/P ratio was calculated by MCA-PI/UA-PI and a ratio of <1.08 was considered abnormal.

Doppler ultrasonography was performed in the last six hours prior to delivery because the IMA level returned to normal after about six hours following reperfusion. Four milliliters of venous blood sample from the umbilical cord was collected in non-heparinized tubes by direct venipuncture of the umbilical vein following double clamping of the cords just after delivery of the neonate. Blood samples were immediately centrifu ged after clotting. The supernatant serum was stored at -80°C until assay. Samples were allowed to clot for 30 min and then centrifuged for 10 min at 3500 rpm. The aliquots of supernatants were stored at-80°Cuntiltesting.Frozen samples were mixed thoroughly after thawing and recentrifuged before analysis. Expressions at the protein level for IMA were determined by means of commercially available ELISA kits The absorbance was measured at 450 nm using a microplate reader. Quantifications were achieved by the construction of standard curves using known concentrations of IMA and the results were expressed in picomoles per milliliter (pmol/mL).

RESULTS

Sixty (18.8%) of a total of 90 neonates were born in complicated pregnancies (Table 1). They had a lower birth weight when compared with neonates in the control group, but no differences were found in other clinical and demographic characteristics between these groups (Table 2). Their mean cord blood serum IMA levels were significantly elevated compared to those from uncomplicated pregnancies (*P<0.001*). The distribution of serum IMA levels between the groups is shown in (Figure 1).

Neonatal asphyxia was diagnosed in a total of 17 (18 %) neonates. In these cases, the mean birth weight was significantly lower than the controls. The cord blood serum IMA levels were also higher in newborns with neonatal asphyxia as compared to healthy controls, and a statistical significant difference was observed (*P=0.015)* (Table 3).

We also investigated normal and complicated pregnancies according to their mean Doppler parameters (Table 4). The mean C/Pratio-PI showed a significant difference between these groups (*P<0.006*). Also, in complicated pregnancies, the percentage of abnormal C/P ratio-PI was significantly higher than in those of the control group (*P<0.016*). There is also significant increase in UA-RI in risk group than control (*p<0.001*).

The neonatal IMA levels was significantly correlate with their antenatal Doppler parameters as there is negative correltion with C/P ratio (*P<0.0058*). Also, there is positive correlation with UA-RI (*p<0.0125*) as shown in (Table 5).There is statistically significant negative correlation between IMA and APGAR score at 5th minute in risk group (Table 6).

The ROC curve of IMA for the prediction of neonatal asphyxia is shown in (Figure 3). Accordingly, the area under curve was 0.705 (*P=0.002*).The optimum diagnostic cut-off value maximizing sensitivity and specificity was detected to be 268.1 pmol/mL, with a sensitivity of 92.86% and a specificity of 67.39%PPV 46.4,NPV 96.9 (Tables 7 and 8 and Figure 3).

Table 1: Complicated pregnancy group

Condition	N	%
DM	14	15%
CH,HTN	17	18%
IUGR	7	7%
DM&IUGR	4	4%
CH.HTN&IUGR	4	4%
Pre eclampsia	8	8%
CH.HTN&DM	5	5%

Table 2: Clinical and demographic features of complicated pregnancies compared with the control group

	Complicated	Study	*P.value*
Maternal age	28.78	28	0.456
Birt weight	3043.35	3505.67	0.001
Gastional age			0.467
Mode of delivery			
L.S.C.S	43	21	0.8701
S,V.D	17	9	
Type of anaestisa			
General	7	3	
Spinal	36	18	0.9660
Non	17	9	
Gender			
Male	28	14	
Female	32	16	1
Neonatal asphyxia	14	3	0.1298
IMA	265.86	163.37	0.001
Gravidity			0.609

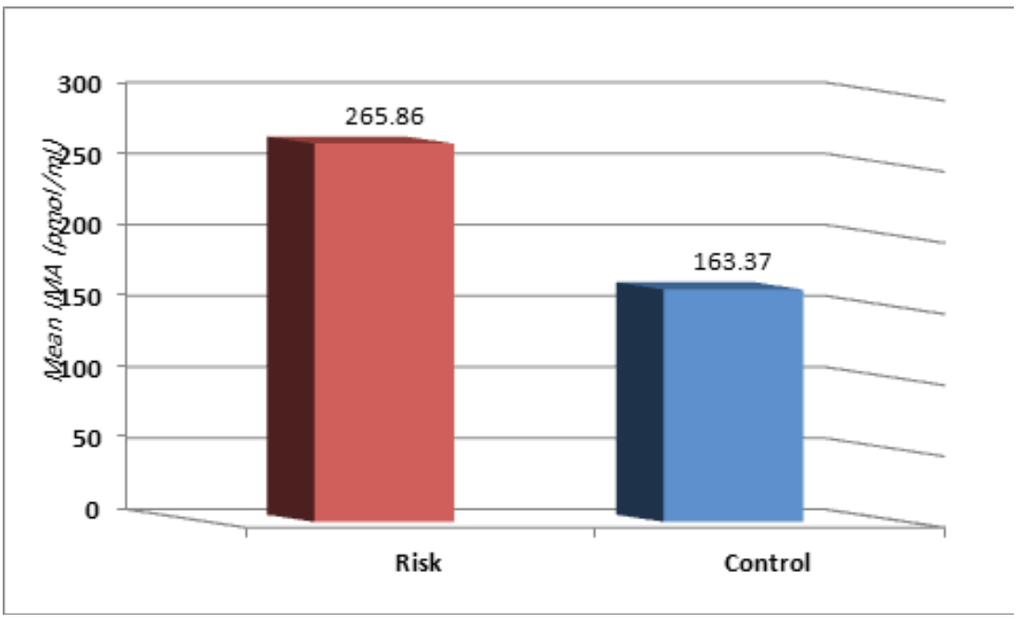

Fig.1: Cord blood serum ischemia-modified albumin (IMA) levels between the study groups

Table 3: Cord blood serum ischemia-modified albumin (IMA) levels between the study groups

	Asphyxia mean	Asphyxia SD	No asphyxia mean	No asphyxia SD	*P .value*
IMA	269.94	2.2715	264.61	6.46	0.004

Table 4: Distribution of antenatal Doppler findings between complicated and uncomplicated pregnancies

	Risk		Control		
Fetal Doppler	Mean	SD	Mean	SD	*P.value*
UA-RI	0.69	0.56	00.56	0.10	0.001
UA-PI	0.84	0.20	00.80	0.17	0.469
MCA-RI	0.99	0.34	00.88	0.23	0.106
MCA-PI	1.05	0.46	11.71	1.98	0.016
C/P ratio	1.26	0.56	22.26	2.61	0.006

Table 5 : Correlation between fetal Doppler and IMA level

Fetal doppler	IMA (pmol/ml)	
	Correlation (r)	*P.value*
UARI	0.139	0.0125
UAPI	-0.016	0.9018
MCARI	-0.200	0.1251
MCAPI	-0.217	0.0963
C/P ratio	-0.183	0.0058

Table 6: correlation between IMA and birth weight and APGAR score at 5th minute

	IMA (Correlation)	IMA (*P.value*)
birth weights	0.059	0.6562
APGAR score at 5th	-0.318	0.0133

Table 7: Predictive value of IMA as a diagnostic marker of neonatal asphyxia in risk group by Receiver Operating Characteristic (ROC) curve analysis

IMA (pmol/ml)	Neonatal asphyxia
Positive group	14 (23.33%)
Negative group	46 (76.67%)
Cut off level	>268.1
Area under curve (AUC)	0.705
Sensitivity (%)	92.86
Specificity (%)	67.39
P. value	0.0018
95% Confidence interval (95% CI)	0.573 to 0.816
Prevalence (%)	23.3
Positive predictive value (PPV)	46.4
Negative predictive value (NPV)	96.9

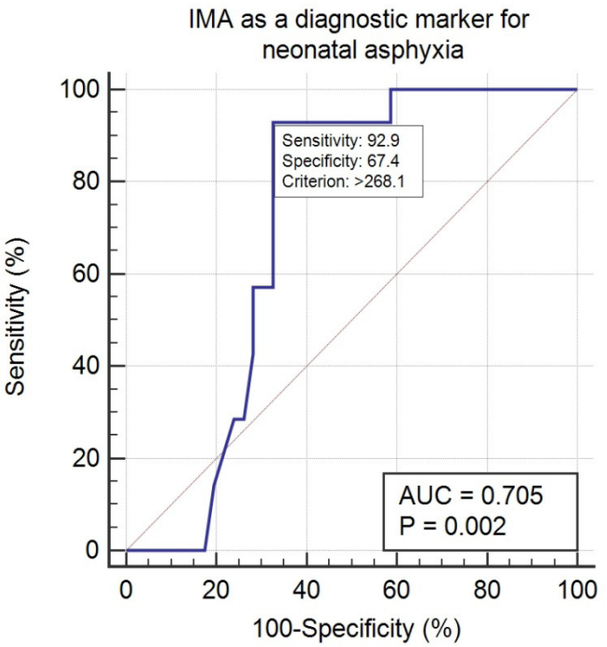

Fig.2: ROC curve for IMA as a predictive marker for neonatal asphyxia

Table 8: IMA as a marker for neonatal asphyxia

IMA	Sensitivity	Specificity	PPV	NPV
≥250.6	100.00	0.00	23.3	
>261.7	100.00	41.30	34.1	100.0
>263.1	92.86	41.30	32.5	95.0
>268.1	92.86	67.39	46.4	96.9
>269.9	57.14	67.39	34.8	83.8
>270.3	57.14	71.74	38.1	84.6
>270.8	42.86	71.74	31.6	80.5
>270.9	28.57	73.91	25.0	77.3
>271.2	28.57	76.09	26.7	77.8
>271.4	21.43	78.26	23.1	76.6
>271.6	14.29	80.43	18.2	75.5
>271.9	0.00	82.61	0.0	73.1
>273.6	0.00	100.00		76.7

DISCUSSION

Neonatal asphyxia is a significant cause of perinatal morbidity and mortality worldwide. It is estimated that around 23% of all newborn deaths are caused by neonatal asphyxia. Each year, between four and nine million newborns develop neonatal asphyxia worldwide, according to the World Health Organization (WHO). It is also estimated that 1.2 million newborn die and at least the same number develop severe complications, such as epilepsy, cerebral palsy, mental retardation, blindness, developmental delay, long-term intellectual impairment and behavioral problems. Despite major advances in monitoring and knowledge of fetal and neonatal physiology and development, neonatal asphyxia remains a serious condition that causes significant mortality and long-term morbidity.

Currently used parameters and markers in daily clinical routine to predict neonatal asphyxia are: Apgar score, umbilical arterial acidemia, base excess, intrapartum electronic fetal monitoring, fetal scalp pH measurement and presence of meconium in amniotic fluid . However, to date no single marker of neonatal asphyxia has shown good predictive efficacy in prediction and early diagnosis of neonatal asphyxia.

In recent clinical studies, it has been found that ischemia-modified albumin (IMA) is a new biochemical marker for the early diagnosis of myocardial ischemic events and cerebrovascular accidents. IMA is a modification of human serum albumin (HSA). Cell membrane integrity is damaged and disrupted by free radicals modifying binding capacity of heavy transition metals suc h as nickel and cobalt at the amino terminal ends of albumin structure. The newly formed albumin with reduced binding capacity to these metals is called ischemic modified albumin (IMA). As a result of an ischemic process, increased levels of IMA have been detected in patients with ischemic heart disease, end-stage renal disease and neonatal asphyxia. Some other diseases caused by ischemia give rise to elevated IMA concentration.

IMA rapidly increases within 5 to 10 min after the ischemic event and remains high for 30 min. It returns to baseline 12 h after the ischemia event, but if the ischemic event persists, it continues to rise[4].

In our study, the primary aim is to evaluate the diagnostic significance of assessing cord blood IMA level in newborns exposed to neonatal asphyxia. We also aimed to determine whether cord blood IMA levels showed a difference between newborns from complicated pregnancies and healthy controls, and to investigate the association of IMA levels with abnormal Doppler findings identified just before delivery in newborns with neonatal asphyxia.

Recently, in two studies among normal pregnancies, it has been demonstrated that maternal serum IMA levels increased to supra-physiological levels in the first trimester of pregnancy compared to non-pregnant controls, and these levels continued to rise from the first trimester to the third trimester[9].

It has been clearly demonstrated that pre-eclampsand chronic hypertention are a disease associated with placental insufficency and increased oxidative stress occurring concurrently with ischemia and associated with increase level of the IMA.

Papageorghiou et al. found that women who developed pre-eclampsia later had higher serum IMA) level sinthe first trimester than those with normal pregnancy[6].

Ustun *et al*., in contrast to results of van Rijn *et al*.[1] demonstrated that IMA levels of pre-eclamptic women were significantly higher than normal controls and were correlated with the severity of pre-eclampsia[2]. However, none of these studies evaluated the IMA levels in newborns.

In a limited study, Gugliucci *et al.* assessed cord blood IMA levels in neonates from complicated deliveries for the first time. Likewise, in our study, we investigated cord blood IMA levels in newborns from complicated pregnancies. In addition, we compared them with cord blood IMA levels from healthy pregnancies. Our complicated group included newborns delivered from pregnancies with pre-eclampsia, diabetes mellitus and IUGR. Although there is no difference for the rate of newborns exposed to perinatal asphyxia between the groups, we found that IMA levels in the complicated group were significantly higher than in the control group.

In the study, we are investigating the association of abnormal Doppler findings with serum levels of IMA. we also compared normal and complicated pregnancies according to antenatal Doppler parameters and we investigated whether their IMA levels showed any correlation with Doppler measurements, especially in complicated pregnancies.

Placental insufficiency is the main cause of fetal hypoxia and IUGR and activates fetal compensatory cardiovascular responses including redistribution of blood flow towards the brain, myocardium and the adrenal glands[10]. This response can be detected by using the C/Pratio.Anabnormal C/P ratio has amore predictive value for perinatal adverse outcomes compared to the assessment of the UA and MCA. Supporting these, we detected that the mean C/P

ratio-PI values were significantly lower in complicated pregnancies than those of the controls. We also observed that the neonatal IMA levels were significantly higher in pregnancies with an abnormal C/P ratio than in the normal groups. The same result was achevied by kumral.

In contrast to Iacovidou *et al*. did not find any difference in cord blood IMA levels between non-distressed IUGR and appropriate for gestational age neonates. These conflicting results may be attributed to the fact that, in our study, the complicated pregnancy group did not encompass only IUGR cases but also include DM and CH.HTN and Pre-eclampsia. As a result, we suggested that neonates from thecomplicated pregnancies presented elevated IMA levels that could indicate an important sub-clinical condition of a fetal or neonatal oxygenation insufficiency and a low-grade inflammatory status.

Therefore, we suggested that IMA level may even be a sensitive marker for newborns with abnormal Doppler findings with neonatal asphyxia or serious hypoxia.

In this study, neonatal IMA levels showed a negative correlation with the C/P ratio-PI, b. However, they have important positive correlations with the UA-RI. Kumral *et al*. showed that IMA level show no correlatin with C/P ratio, and UA-RI but show posistive correlation with UA-PI. Cord blood IMA levels seem to be associated with the mode of delivery. Iacovidou *et al*. reported that IMA levels in cord blood were increased in cases of elective cesarean section compared to cases of vaginal delivery in contrast to or study which show no differnces between both groups[8].

CONCLUSION

The cord blood IMA levels were increased in the newborns from complicated pregnancies. Newborns with neonatal asphyxia had significantly higher serum IMA levels than the non-asphyctic ones.The new borns who underwent the 'brain-sparing effect' shown by an abnormal C/P ratio in antenatal. Doppler examinations were associated with elevated cord blood IMA levels. We may accept elevated cord blood IMA levels as a novel, useful marker in neonatal asphyxia.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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