The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: 1476-7058 (Print) 1476-4954 (Online) Journal homepage: http://www.tandfonline.com/loi/ijmf20

Maternal and umbilical cord ischemia-modified albumin levels in nonreassuring fetal heart rate tracings regarding the mode of delivery

Gamze S. Caglar, Yasemin Tasci, Umit Goktolga, Efser Oztas, Recai Pabuccu, Elif D. Ozdemir & Rabia Seker

To cite this article: Gamze S. Caglar, Yasemin Tasci, Umit Goktolga, Efser Oztas, Recai Pabuccu, Elif D. Ozdemir & Rabia Seker (2013) Maternal and umbilical cord ischemia-modified albumin levels in nonreassuring fetal heart rate tracings regarding the mode of delivery, The Journal of Maternal-Fetal & Neonatal Medicine, 26:5, 528-531, DOI: 10.3109/14767058.2012.743519

To link to this article: https://doi.org/10.3109/14767058.2012.743519

Accepted author version posted online: 31 Oct 2012.
Published online: 15 Nov 2012.

The Journal of Maternal-Fetal and Neonatal Medicine, 2013; 26(5): 528–531

ISSN 1476-7058 print/ISSN 1476-4954 online
DOI: 10.3109/14767058.2012.743519

informa
healthcare

Maternal and umbilical cord ischemia-modified albumin levels in nonreassuring fetal heart rate tracings regarding the mode of delivery

Gamze S. Caglar[1], Yasemin Tasci[2], Umit Goktolga[2], Efser Oztas[1], Recai Pabuccu[1], Elif D. Ozdemir[1] & Rabia Seker[3]

[1]Ufuk University School of Medicine, Department of Obstetrics and Gynecology, Ankara, Turkey, [2]Ministry of Health, Etlik Zübeyde Hanım Womens Health Research Hospital, Department of Obstetrics and Gynecology, Ankara, Turkey, and [3]Ufuk University School of Medicine, Department of Biochemistry, Ankara, Turkey

***Objective*: To evaluate umbilical cord blood ischemia-modified albumin (IMA) levels in cases of fetal distress (FD) and to explore fetal blood IMA levels regarding the route of delivery. *Methods*: Umbilical cord and maternal serum IMA concentrations were assessed in term 40 cases with cesarean section (CS) due to FD, 76 cases with elective repeat CS and 85 cases with noncomplicated vaginal delivery. *Results*: The maternal and umbilical cord IMA levels were significantly lower in vaginal deliveries when compared with CS cases either in FD or previous CS groups ($p = 0.02$). Although no statistically significant difference was found in IMA levels of CS groups (previous CS vs. FD), cord blood IMA levels tend to be higher in FD group. Neither demographic characteristics nor fetal outcome parameters were found to have any correlation with maternal IMA levels. However, umbilical cord IMA levels were found to be negatively correlated with 1th min Apgar scores ($r = -0.143$, $p = 0.043$). *Conclusions*: IMA seems to be responsive to hypoxic FD showing the highest levels in cases with severe fetal hypoxia. Higher levels of IMA in cases with elective repeat CS might indicate acute transient hypoxia and possible myocardial ischemia in these cases.**

Keywords: Ischemia-modified albumin, fetal distress, elective repeat cesarean section

Introduction

The assessment of fetal well being is the major issue in intrapartum obstetric practice which can be evaluated by intermittent auscultation, cardiotocography (CTG) and intermittent fetal blood sampling [1]. All these methods aid the clinician to deliver the baby before any damage or death occurs. CTG is a widely employed method that assesses fetal oxygenation indirectly and noninvasively [1]. First aim of fetal heart rate (FHR) monitoring is to identify hypoxemic and acidotic fetuses to prevent fetal death and the second is to avoid fetal neurologic injury, if possible. As the fetal brain modulates fetal heart, FHR monitoring is an indirect way of measuring fetal cardiac and medullary responses to changes in fetal blood volume and hypoxemia/acidemia [2]. Cardiovascular response to severe hypoxia results in persistent bradycardia or repetitive late decelerations related to myocardial depression [2].

Not all cases requiring intervention due to abnormal FHR results in severely hypoxic, acidotic newborns [3,4]. Therefore, nonreassuring fetal status necessitates assessment of fetal acidosis. A nonreassuring FHR pattern can reverse or improve by nonsurgical first step interventions (oxygen administration, lateral positioning, hydration, discontinuing oxytocin, use of tocolytics) [5], all aiming to improve fetal oxygenation by adjusting uteroplacental perfusion. If these measures does not help, then any attempt to rule out metabolic acidosis should be performed. Operative delivery is required in cases where metabolic acidosis can not be ruled out or the decelerations persist [5].

Ischemia-modified albumin (IMA) is a marker of oxidative stress approved from FDA for the diagnosis of cardiac ischemia in adults [6]. Although better studied in acute coronary diseases [7], IMA was recently studied in maternal serum and umbilical cord blood [8–10]. In our study, umbilical cord blood IMA levels were evaluated to detect fetal tissue ischemia in cases with prolonged/late decelerations. Moreover, this study also evaluates maternal and fetal blood IMA levels regarding the route of delivery (vaginal vs. cesarean section (CS)) which might also alter the results. As far as we know this is the first study in the literature evaluating IMA levels in umbilical cord blood of fetuses with nonreassuring FHR tracings and the association with Apgar scores and neonatal outcome.

Materials and methods

This cross-sectional study was performed between 1 November 2009 and 1 August 2010 in two institutions (a university hospital and the other research hospital). The study was approved by the research ethic committees of the participating institutions. Participants were women in labor admitted for delivery with uncomplicated term gestations with fetus in cephalic presentation. All patients gave informed consent before enrollment. Initially, obstetric ultrasound were performed to confirm gestational age and to determine the amniotic fluid volume, the lie and position of the fetus. The exclusion criteria composed of complicated pregnancies (e.g. intrauterine growth retardation, gestational diabetes mellitus, preeclampsia, fetal congenital malformation, oligohydramnios-defined as deepest vertical pocket of amniotic fluid <2 cm, placenta previa), mothers with chronic illnesses (e.g. hypertension, diabetes mellitus) and any history of cardiac symptoms, angina, myocardial infarction, coronary artery disease. In addition, smokers, alcohol consumers and multiple pregnancies were also excluded from the study.

At the time of enrollment, all were having spontaneous onset of labor with painful, regular uterine contractions with cervical

Correspondence: Dr Yasemin Tasci, Ministry of Health, Etlik Zübeyde Hanım Womens Health Research Hospital, Department of Obstetrics and Gynecology, Etlik, 06010, Ankara, Turkey. Tel.: 90 312 567 4456; Fax: 90 312 3238191. E-mail: yytasci@yahoo.com

effacement, bloody show, with or without rupture of membranes. Amniotomy was performed when the cervix was 3 cm dilated. All women were having spontaneous contractions of adequate frequency. Augmentation with oxytocin was not applied to any of the cases. Neither epidural analgesia nor opioids were used for pain relief. Continue external fetal monitorization was applied to all fetuses. Hourly visits and care in the event of nonreassuring FHR pattern was performed by the same obstetricians in charge. In cases with persistant late decelerations (>50% of contractions) or those with recurrent prolonged decelerations (≥2 below 70 beats/min for >90 s) the following steps were performed for the management of these patterns [5]. Maternal blood pressure was measured to rule out the hypotension; oxygen by face mask was applied; laterally positioning of the mother was performed; intravenous hydration was given. CS was performed in <30 min of decision of delivery under general anesthesia, if decelerative pattern persists. Cases with reassuring FHR pattern through labor delivered vaginally.

Controls with previous CS were scheduled for delivery at 39 weeks of gestation (n = 76). All were without medical complications with a singleton fetus in a vertex presentation. After informed consent, CS was performed by the same operators under spinal anesthesia.

Maternal blood samples were collected from antecubital vein into a nonheparinized tube in the maternity ward before any intervention. Cord blood was collected at birth, from the double-clamped umbilical cord that reflects the fetal state. Samples were immediately centrifuged, and serum was separated and frozen at –80°C until assay. IMA concentrations were analyzed by measuring the complex composed of dithiothreitol (DTT) and cobalt unbind to albumin by colorimetric method in spectrophotometer. The analyses in spectrophotometer (Human Humalyzer 2000) was performed at 470 nm for detection of absorbance of the specimens and the results were given as absorbance units (ABSU).

The clinical outcome of the fetus was evaluated in the 1st and 5th min after birth according to the Apgar score. The infants with jaundice, seizures, treatment for sepsis, resuscitation at birth, or admission to the neonatal intensive care unit (NICU) were recorded.

Statistical analyses

Data analysis was performed by using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA). The mean differences between groups were compared by Student's t-test. Mann–Whitney U-test was applied for the comparisons of the median values. Nominal data were analyzed by χ^2 or Fisher's exact test, where appropriate. Multiple logistic regression analysis was used to determine the independent predictors which mostly affected on IMA levels. Any variable whose univariable test had a p value <0.25 was accepted as a candidate for the multivariable model along with all variables of known clinical importance. Odds ratio and 95% confidence intervals for independent variables were calculated. A p value <0.05 was considered statistically significant.

Results

During the study period 391 women were eligible for the study, of whom 235 (%60.1) agreed to participate. Among these cases 76 women with previous CS scheduled constitute the controls. In 159 cases admitted with spontaneous onset of delivery, 34 (21.3%) cases required augmentation with oxytocin due to inefficient uterine contractions and were excluded from the study. In the remaining 125 cases 85 (68%) delivered vaginally. Among vaginal deliveries 6 (3.7%) cases had decelerations during labor and initial nonsurgical steps helped to resolve decelerations and all delivered vaginally. In 40 cases (32%) CS was performed due to FD.

The mean age of the women were 28.1 ± 5.1 years; mean gestational age at delivery were 39.1 ± 1.0 weeks and the median of gravidity were 2 (minimum 1 – maximum 6) and mean maternal blood IMA levels were 0.62 ± 0.1 ABSU. Maternal IMA levels were significantly lower in vaginal deliveries when compared with CS cases either in FD or previous CS groups (p = 0.02). None of the cases had any maternal complications during labor and delivery. The demographic data of the groups is given in Table I.

Mean birth weight of the infants were 3,336 ± 376 g. No significant difference were found in birth weight or fetal sex of infants when three groups were compared (p > 0.05). The gestational age at delivery, fetal outcome evaluated by Apgar scores, mean levels of umbilical cord IMA levels and the rate of NICU admission are given in Table II.

Two neonates, one in FD group and done in vaginal delivery group, had an Apgar scores at 5 min of age <7. None required resuscitation at birth. Neither seizures nor sepsis was observed in any of the neonates. Treatment for neonatal jaundice was performed to 14 neonates. Three neonates (one case from each group) were admitted to the NICU for transient tachypnea. The follow-up of all neonates were uneventful.

The multiple logistic regression analysis was performed to determine the independent predictors which mostly affected on IMA levels. Neither demographic characteristics (age, gravidity, parity, gestational age at birth) nor fetal outcome parameters (Apgar scores, birth weight, fetal complications) were found to have any correlation with maternal IMA levels. However, umbilical cord IMA levels were found to be negatively correlated with 1th min Apgar scores (r = –0.143, p = 0.043).

Discussion

In this study, the results show that reduced blood flow to the fetus might cause IMA generation. Fetal tissue ischemia detected by umbilical cord IMA levels is significantly higher in cases with late or prolonged decelerations. This is the first study in the literature documenting cord blood IMA levels in nonreassuring FHR tracings.

During ischemia, acidosis and generation of superoxide free radicals reduces the ability of albumin to take up metal ions such as cobalt, copper, and nickel. As a result of oxidative stress, the N-terminal portion of the human serum albumin becomes unable

Table I. Maternal characteristics.

Parameter	Previous CS n = 76	Fetal distress n = 40	Vaginal delivery n = 85	p
Age (years) Mean ± SD	27.9 ± 4.8	27.7 ± 5.5	26.9 ± 4.9	NS
Gravidity Median (min–max)	2 (1–5)	1 (1–6)	2 (1–6)	p < 0.05*
Parity Median (min–max)	1 (0–3)	0 (0–3)	0 (0–3)	p < 0.05*
Maternal IMA levels (ABSU)	0.65 ± 0.15	0.67 ± 0.17	0.58 ± 0.16	p < 0.05*

ABSU, absorbance units; CS, Cesarean section; IMA, ischemia-modified albumin; NS, not significant.
*Statistically significant.

Table II. Fetal outcome and complications.

Parameter	Previous CS $n = 76$	Fetal distress $n = 40$	Vaginal delivery $n = 85$	p
Gestational age at delivery (weeks)	39.7 ± 0.8	39.2 ± 1.0	39.3 ± 1.2	NS
Birth weight(g)	3349 ± 398	3313 ± 384	3336 ± 356	NS
Mean ± SD				
1'Apgar	9 (6–9)	9 (4–9)	9 (4–9)	NS
Median (min–max)				
5'Apgar	10 (8–10)	10 (9–10)	9 (7–10)*	NS
Median (min–max)				
NICU admission	7 (9.2)	3 (7.5)	7 (8.2)	NS
n (%)				
Umbilical cord IMA (ABSU)	0.60 ± 0.1	0.66 ± 0.1	0.52 ± 0.1*	<0.05*
Mean ± SD				

ABSU, absorbance units; CS, Cesarean section; NICU, neonatal intensive care unit; NS, not significant.
*Statistically significant.

to bind metal ions and IMA generation occurs [11]. Therefore, IMA is an end product of oxidative stress lacking tissue specificity [11]. Although IMA is mostly studied in cardiac events, ischemia in any organ before infarction can lead to IMA elevation within 6–10 min and remains positive up to 6 h [11]. Elevations in serum IMA levels may occur in increasing number of clinical conditions associated with oxidative stress apart from acute coronary syndrome [11]. Elevated IMA levels after strenuous physical exercise, tourniquet application during surgery and arterial clamping during revascularization procedures are some of these conditions reported in the literature [12,13].

The data in the literature concerning IMA levels in perinatal period is very limited. In a previous study [8] with very few number of cases, the cord blood IMA levels of 12 normal term deliveries were significantly lower than cord blood levels of neonates from 14 complicated labors. Other than the elevated IMA levels in complicated deliveries, Iacovidou et al. [9] evaluated cord blood IMA levels in nondistressed intrauterine growth retarded fetuses. No significant difference in IMA levels between appropriate for gestational age and IUGR fetuses was found [9]. Our study presents a slightly increased IMA level in cord blood of babies delivered with CS because of signs of fetal distress (FD) compared to vaginally delivered control babies. Early tissue ischemia of the fetal liver, kidney, or skeletal muscle might be any of the possible candidates responsible for the elevated IMA levels in FD group of this study since IMA is a nonspecific reaction to tissue hypoxia–ischemia.

Lack of assessment of fetal acidosis is a limitation of this study. But the accuracy of intermittent fetal scalp pH assessment for predicting neonatal acidosis with subsequent neurologic sequela has been questioned and it is no longer used in many institutions because of poor sensitivity and positive predictive value for predicting umbilical arterial pH <7 and for identifying newborns with hypoxic–ischemic encephalopathy [14]. In our study, only two of the neonates had Apgar scores at 5 min of age <7 and none required resuscitation at birth. The negative correlation between cord IMA and 1 min Apgar score in this study has a low r value. Since one minute Apgar score is an indicator of neonatal vigilance but a very poor indicator of intrapartum asphyxia and IMA is a nonspecific reaction to tissue hypoxia–ischemia, such a correlation would rather be confirmed in larger studies including a high-risk obstetric material and by adding the measurement of umbilical cord blood acid-base status.

Significantly higher levels of cord blood IMA in elective CS cases when compared to vaginal deliveries was reported previously [9], supporting our results. The authors suggested higher oxidative stress as a cause of elevated IMA levels in elective CS cases [9]. Another explanation might be a transient localized tissue ischemia due to the external forces exerted on the fetus or anesthetic interventions during CS. CS per se, either for previous CS or for FD, under anesthesia might elevate IMA levels causing hypotension and uterine hypoperfusion which is a very similar mechanism as in tourniquet and revascularization surgery reports. Normal pregnancy is characterized by significant maternal adaptive response, and production of many pro-oxidant and vasoactive substances by the placenta. In fact, oxidative stress in the fetal circulation does not depend on the mode of delivery [15].

As a noninvasive direct measure of fetal acid-base status does not exist, CTG is still the standard approach. This is the first study in the literature documenting cord blood IMA levels in nonreassuring FHR tracings. Elevated IMA levels in cases with late or prolonged decelerations may indicate fetal tissue ischemia in the neonate. Though, cord blood IMA levels is a marker of transient ischemia, the unknown long term consequences of neonates with high IMA level necessitates follow-up of these children.

Declaration of Interest: The authors report no declaration of interest.

References

1. Freeman RK. Problems with intrapartum fetal heart rate monitoring interpretation and patient management. Obstet Gynecol 2002;100:813–826.
2. Westgate JA, Wibbens B, Bennet L, Wassink G, Parer JT, Gunn AJ. The intrapartum deceleration in center stage: a physiologic approach to the interpretation of fetal heart rate changes in labor. Am J Obstet Gynecol 2007;197:236.e1–236.11.
3. Nelson KB, Dambrosia JM, Ting TY, Grether JK. Uncertain value of electronic fetal monitoring in predicting cerebral palsy. N Engl J Med 1996;334:613–618.
4. Parer JT, King T. Fetal heart rate monitoring: is it salvageable? Am J Obstet Gynecol 2000;182:982–987.
5. Macones GA, Hankins GD, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines. Obstet Gynecol 2008;112:661–666.
6. Lippi G, Montagnana M, Guidi GC. Albumin cobalt binding and ischemia modified albumin generation: an endogenous response to ischemia? Int J Cardiol 2006;108:410–411.
7. Sinha MK, Roy D, Gaze DC, Collinson PO, Kaski JC. Role of "Ischemia modified albumin", a new biochemical marker of myocardial ischaemia, in the early diagnosis of acute coronary syndromes. Emerg Med J 2004;21:29–34.
8. Gugliucci A, Hermo R, Monroy C, Numaguchi M, Kimura S. Ischemia-modified albumin levels in cord blood: a case-control study in uncomplicated and complicated deliveries. Clin Chim Acta 2005;362:155–160.
9. Iacovidou N, Briana DD, Boutsikou M, Liosi S, Baka S, Boutsikou T, Hassiakos D, Malamitsi-Puchner A. Cord blood ischemia-modified albumin levels in normal and intrauterine growth restricted pregnancies. Mediators Inflamm 2008;2008:523081.
10. van Rijn BB, Franx A, Sikkema JM, van Rijn HJ, Bruinse HW, Voorbij HA. Ischemia modified albumin in normal pregnancy and preeclampsia. Hypertens Pregnancy 2008;27:159–167.
11. Gaze DC. Ischemia modified albumin: a novel biomarker for the detection of cardiac ischemia. Drug Metab Pharmacokinet 2009;24:333–341.
12. Apple FS, Quist HE, Otto AP, Mathews WE, Murakami MM. Release characteristics of cardiac biomarkers and ischemia-modified albumin as

measured by the albumin cobalt-binding test after a marathon race. Clin Chem 2002;48:1097–1100.
13. Refaai MA, Wright RW, Parvin CA, Gronowski AM, Scott MG, Eby CS. Ischemia-modified albumin increases after skeletal muscle ischemia during arthroscopic knee surgery. Clin Chim Acta 2006;366:264–268.
14. Kruger K, Hallberg B, Blennow M, Kublickas M, Westgren M. Predictive value of fetal scalp blood lactate concentration and pH as markers of neurologic disability. Am J Obstet Gynecol 1999;181(5 Pt 1):1072–1078.
15. Fogel I, Pinchuk I, Kupferminc MJ, Lichtenberg D, Fainaru O. Oxidative stress in the fetal circulation does not depend on mode of delivery. Am J Obstet Gynecol 2005;193:241–246.