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The impact of nuchal cord on umbilical cord blood gas analysis and ischaemia-modified albumin levels in elective C-section

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ABSTRACT
This study was designed to evaluate umbilical cord ischaemia-modified albumin (IMA) levels and the cord blood gas parameters of foetuses with or without nuchal cords, at the time of elective C-section. The cross-sectional study population consisted of the patients who were admitted to the Tertiary Care Center between February and June 2015. Women with uncomplicated single term gestations between 37 and 40 completed weeks and scheduled for elective C-sections were included in the study. Fifty cases with a nuchal cord and 50 cases without a nuchal cord were recruited. Nuchal cord blood gas analysis and the IMA levels were evaluated. The IMA levels in umbilical artery of foetuses both in the study and control groups were similar (0.714 ± 0.150 vs. 0.689 ± 0.107 ABSU, \( p = .340 \), respectively). The umbilical artery pH values of the study group were significantly lower than that in the control group (7.31 ± 0.04 vs. 7.32 ± 0.03, \( p = .042 \); respectively). The results of the current study indicate that the nuchal cord has an impact on the foetal cord blood gas parameters to some extent before the initiation of labour. Fortunately, this impact does not end up with foetal tissue ischaemia, as confirmed by the IMA levels.

IMPACT STATEMENT

- What is already known on this subject? The impact of nuchal cord on perinatal outcomes has been the subject of research for many years. Although the accumulated data has pointed out some unfavourable perinatal effects, the heterogeneity of the study groups both including a vaginal delivery and C-section and the inability to adjust the interfering factors ended up with some controversies. This is why there is not much known about the effects of the nuchal cord in women who are not in the labour process.

- What do the results of this study add? The current study aimed to exclude the interfering effects such as the active stage of labour. In this study, elective caesarean sections were selected as the study population to evaluate the effects of the nuchal cord on cord blood gas parameters and the IMA values. pH analysis in cord blood is used to detect hypoxia and the IMA is a new ischaemia marker. The results revealed that the in utero nuchal cord is associated with a significantly higher pCO2 and lower pH values and similar IMA values.

- What are the implications of these findings for clinical practice and/or further research? The final outcome supports that the nuchal cord causes alterations in cord blood gas analysis but this does not reach critical levels. Therefore, the results show that there is no need to change clinical practice when the nuchal cord is detected by ultrasound in a term gestation.

Introduction

Ischaemia-modified albumin (IMA) is the modified form of albumin generated as a result of oxidative stress following ischaemia, which causes changes in N-terminus (Bar-Or et al. 2001). IMA has been certified by the United States Food and Drug Administration (FDA) for use in cardiac pathologies as an early marker of ischaemia (Wu 2003). Besides, IMA has also been reported to increase in other ischaemic conditions, such as perinatal complications (Yarcı Gursoy et al. 2017). The levels of IMA in maternal and cord bloods have been the focus of research in pregnancies complicated with intrauterine growth restriction (Guvendag Guven et al. 2013; Kiseli et al. 2015); acute foetal distress (Caglar et al. 2013) and with preeclampsia (Papageorghiou et al. 2008; Ustun et al. 2011). In the above-mentioned conditions diminished uteroplacental perfusion and foetal oxygenation has been associated with increased levels of IMA in cord blood. Likewise, umbilical cord blood flow, if partially or intermittently obstructed may result in decreased foetal oxygenation (Martin et al. 2005).

The umbilical cord loops around the neck (nuchal cord) is a quite frequent situation, with an incidence ranging between...
15.8% and 30% in the late trimesters of pregnancy (Clapp et al. 1999; Assimakopoulos et al. 2005) and the clinical significance of this situation is controversial. Nearly six decades ago, Shui and Eastman (Shui and Eastman 1957) demonstrated for the first time in the literature that, the presence of a nuchal cord at a delivery did not increase the perinatal mortality, which was later supported by other authors (Clapp et al. 1999; Qin et al. 2000; Mastrobattista et al. 2005; Sheiner et al. 2006). On the other hand, in the 1990s, numerous studies reported that a nuchal cord is associated with various problems in the first and second stages of labour and with adverse perinatal outcomes, such as the increased incidence of variable decelerations (Tejani et al. 1977), meconium-stained amniotic fluid (Jauniaux et al. 1995), low Apgar scores (Larson et al. 1995; Clapp et al. 1999; Assimakopoulos et al. 2005), cerebral palsy (Clapp et al. 1999) and umbilical artery acidaemia (Hankins et al. 1987).

Although, the clinical significance of such a frequent clinical condition still needs to be elucidated, the presence of the nuchal cord in labour and delivery has been associated with adverse neonatal outcomes. The recent data indicate that nuchal cords during labour and a vaginal delivery may cause decreased foetal perfusion (Martin et al. 2005).

The effect of this clinical condition on foetal well-being has been evaluated previously with parameters such as Apgar scores (Clapp et al. 1999; Assimakopoulos et al. 2005), a neonatal intensive care unit submission (Jauniaux et al. 1995), as well as cord blood gas analyses (Onderoglu et al. 2008). However, IMA, a new and potential ischaemia marker in perinatology, has never been used for evaluating the foetal well-being in foetuses with a nuchal cord. Moreover, the previous studies concerning the effect of a nuchal cord on a cord blood gas analysis have included mostly heterogeneous populations of women delivering by either vaginal route or by a C-section. In order to exclude the possible interfering effect of the labour process in the presence of nuchal cord, this study is designed to evaluate umbilical cord IMA levels and cord blood gas analysis of foetuses with or without nuchal cords during an elective C-section.

Materials and methods

The cross-sectional study was conducted in a Tertiary Care Center between February and June, 2015. The study was approved by the Ethical Committee and an informed consent was taken from the participants. Women with uncomplicated single term gestations between 37 and 40 completed weeks and scheduled for elective C-section either due to a repeat C-section or foetal malpresentation were offered to participate in the study. Among the participants who were found to have at least one nuchal cord around the foetal neck during C-section constituted the study group and the others who were found not to have a nuchal cord were recruited for the control group. The gestational age was determined according to the ultrasonographic examination performed between the 11th and 14th weeks of gestation. Pregnant women, with chronic hypertension, preeclampsia, intrauterine growth restriction, pregestational or gestational diabetes mellitus, who are smokers, whose maternal age is <18 and >35, who have placental insertion abnormalities, preterm deliveries (<37 weeks), maternal chronic diseases with or without any medication supplementation and who were having emergency caesarean sections due to uterine contractions were excluded.

Data of 100 women, 50 in study and 50 in control group, were included in the analysis. Maternal venous blood samples for IMA measurements were collected in the theatre room just before any intervention. The umbilical artery blood samples, both for blood gas analysis and IMA, were collected from the umbilical artery just after the delivery of the foetus. The blood gas analysis was evaluated just at the theatre room by Radiometer ABL 800 Basic (Radiometer, Copenhagen, Denmark). The blood samples in plain tubes taken for IMA analysis were centrifuged within one hour after their collection and sera were separated and stored at −80°C. All the samples of maternal and cord blood were analysed in a single run. The IMA concentrations were analysed by measuring the complex, composed of diithiothreitol and cobalt (Sigma Aldrich®, St Louis, MO) and unbound to albumin by the colourimetric method in a spectrophotometer. The analyses in the spectrophotometer (Human Humalyzer®, 2000, Wiesbaden, Germany) were performed at 470 nm for the detection of the absorbance of the specimens, and the results were given in absorbance units (ABSU).

Statistical analyses

The statistical analysis was performed with IBM SPSS for Windows Version 21.0 software. Numerical variables were expressed as the mean ± standard deviation or median [min.–max.] as appropriate. The categorical variables were presented as numbers and percentages. Normality of the continuous variables was tested by the Shapiro–Wilks test. The Levene test was used to show the homogeneity of the variances. The independent samples t-test or the Mann–Whitney U test was used to determine the difference between the two independent groups according to the parametric test assumptions. More than two independent groups were compared by one-way ANOVA or by use of the Kruskal Wallis test, as appropriate. The categorical variables were compared by the Chi square or the Fisher exact test. A p value of <.05 was considered as statistically significant.

Results

The demographic variables including the age, gravidity, parity, body mass index, biochemical parameters and the complete blood count parameters were similar between the two groups (Table 1). IMA levels in maternal blood and umbilical artery of the foetuses were similar between the study and control groups (p = .745 and p = .340, respectively). None of the foetuses suffered from foetal umbilical artery acidaemia, which is defined as a pH value <7.0 by Task Force on Neonatal Encephalopathy (ACOG 2014). The umbilical artery pH values of the study group were significantly lower than the control group (p = .042) whereas the pCO₂ levels were significantly higher in study group compared to the controls.
Table 1. Demographic parameters and laboratory values of groups.

<table>
<thead>
<tr>
<th></th>
<th>Study group (n = 50)</th>
<th>Control group (n = 50)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>28.6 ± 4.8</td>
<td>27.9 ± 5.2</td>
<td>.499</td>
</tr>
<tr>
<td>Parity</td>
<td>1 [0–2]</td>
<td>1 [0–4]</td>
<td>.899</td>
</tr>
<tr>
<td>Abortus</td>
<td>0 [0–1]</td>
<td>0 [0–2]</td>
<td>.688</td>
</tr>
<tr>
<td>Children</td>
<td>1 [0–2]</td>
<td>1 [0–4]</td>
<td>.726</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>30.6 ± 3.2</td>
<td>30.4 ± 3.3</td>
<td>.766</td>
</tr>
<tr>
<td>pCO₂ (mmHg)</td>
<td>42.5 ± 5.3</td>
<td>45.4 ± 5.6</td>
<td>.026</td>
</tr>
<tr>
<td>(mmol/L)</td>
<td>[0.80–1.10]</td>
<td>[0.80–1.10]</td>
<td></td>
</tr>
<tr>
<td>lactic acidosis</td>
<td>203,380 ± 55,942</td>
<td>191,780 ± 42,280</td>
<td>.245</td>
</tr>
<tr>
<td>(ABSU)</td>
<td>0.714 ± 0.150</td>
<td>0.689 ± 0.107</td>
<td>.340</td>
</tr>
<tr>
<td>Maternal IMA (ABSU)</td>
<td>0.701 ± 0.140</td>
<td>0.710 ± 0.137</td>
<td>.745</td>
</tr>
<tr>
<td>Base deficit (mmol/L)</td>
<td>3.10 ± 0.10</td>
<td>3.35 ± 0.40</td>
<td>.042</td>
</tr>
<tr>
<td>WBC (/μL)</td>
<td>11,876 ± 1938</td>
<td>11,676 ± 1928</td>
<td>.434</td>
</tr>
<tr>
<td>Plt (/μL)</td>
<td>203,380 ± 55,942</td>
<td>191,780 ± 42,280</td>
<td>.245</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>11.8 ± 1.4</td>
<td>11.6 ± 1.5</td>
<td>.434</td>
</tr>
<tr>
<td>Foetal birthweight (g)</td>
<td>3265.6 ± 343.3</td>
<td>3348.8 ± 358.1</td>
<td>.239</td>
</tr>
<tr>
<td>pH</td>
<td>7.31 ± 0.04</td>
<td>7.32 ± 0.03</td>
<td>.042</td>
</tr>
<tr>
<td>Foetal cord pH</td>
<td>7.31 ± 0.04</td>
<td>7.32 ± 0.03</td>
<td>.042</td>
</tr>
<tr>
<td>Foetal gender (F/M)</td>
<td>28/22</td>
<td>29/22</td>
<td>.318</td>
</tr>
<tr>
<td>Antenatal IMA (ABSU)</td>
<td>0.701 ± 0.140</td>
<td>0.710 ± 0.137</td>
<td>.745</td>
</tr>
<tr>
<td>pO₂ (mmHg)</td>
<td>21.8 ± 5.0</td>
<td>21.8 ± 5.0</td>
<td>.091</td>
</tr>
</tbody>
</table>

BMI: body mass index; WBC: white blood count; Hb: haemoglobin; Plt: platelet; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BUN: blood urea nitrogen; IMA: ischaemia-modified albumin; ABSU: absorbance unit.

Table 2. Comparison of maternal and foetal IMA values and cord blood gas parameters in control, nuchal cord with one or more loops.

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 50)</th>
<th>Nuchal cord (1 Loop) (n = 31)</th>
<th>Nuchal cord (&gt;1 Loop) (n = 19)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal IMA (ABSU)</td>
<td>0.710 ± 0.137</td>
<td>0.701 ± 0.143</td>
<td>0.701 ± 0.139</td>
<td>0.948</td>
</tr>
<tr>
<td>Umbilical artery IMA (ABSU)</td>
<td>0.689 ± 0.107</td>
<td>0.704 ± 0.168</td>
<td>0.729 ± 0.115</td>
<td>0.512</td>
</tr>
<tr>
<td>pH</td>
<td>7.32 ± 0.03</td>
<td>7.31 ± 0.04</td>
<td>7.31 ± 0.03</td>
<td>0.128</td>
</tr>
<tr>
<td>Base deficit (mmol/L)</td>
<td>3.35</td>
<td>3.05</td>
<td>3.40</td>
<td>0.760</td>
</tr>
<tr>
<td>pCO₂ (mmHg)</td>
<td>42.5 ± 5.3</td>
<td>45.4 ± 5.6</td>
<td>45.6 ± 4.7</td>
<td>0.026</td>
</tr>
<tr>
<td>pO₂ (mmHg)</td>
<td>21.8 ± 5.0</td>
<td>21.8 ± 5.0</td>
<td>21.5 ± 4.6</td>
<td>0.091</td>
</tr>
</tbody>
</table>

MA: ischaemia-modified albumin; ABSU: absorbance unit.

*Control group is significantly different than both study groups (1 Loop and >1 Loop).

(p = .005). The base deficit and pO₂ values were similar between the two groups (p > .05). In the study group 31 (62%) of the foetuses had one nuchal loop, whereas 19 (38%) foetuses had more than one loop (13 foetuses had two and six foetuses had three loops). Regarding the number of nuchal loops, pH values, base deficits and umbilical cord IMA levels were not different between the cases with one or more than one nuchal loop and controls (Table 2).

**Discussion**

The results of this study show that the existence of a nuchal cord is associated with lower cord blood pH levels, which do not go beyond the accepted clinically significant values. Moreover, the foetuses with or without a nuchal cord demonstrated similar cord blood IMA levels. This is the first study evaluating the IMA levels in foetuses with a nuchal cord delivered by an elective C-section. The current data supports that, although a nuchal cord has an effect on cord blood gas parameters to some extent, the parameters remain in the normal range, so were clinically negligible for this study. Besides, the absence of significant difference between IMA values between study and control groups supports these outcomes.

To-date, lower umbilical artery pH values in the presence of a nuchal cord has been reported by numerous authors (Hankins et al. 1987; Larson et al. 1995; Onderoglu et al. 2008; Bernad et al. 2012; Narang et al. 2014). However, many of the previous studies included heterogeneous groups of women who delivered by vaginal route, by an elective C-section or an emergency C-section, revealing inconsistent results, although, the cord blood pH values at delivery might be affected by the dynamics of the labour. Moreover, the unfavourable factors (e.g. meconium-stained amniotic fluid, operative delivery) associated with the lower pH values complicating the delivery have been reported to be more frequently observed in foetuses with a nuchal cord (Stembera and Horska 1972; Hankins et al. 1987; Larson et al. 1995; Assimakopoulos et al. 2005; Onderoglu et al. 2008; Nkwabong and Fomulu 2011). Therefore, in order to discriminate the impact of nuchal cord per se on the cord blood IMA levels, women who delivered by an elective C-section were recruited in this study. In this group of pregnant women, the pH values of the cord blood have been shown to be significantly lower, but still remaining in the normal range. Whether this result has any clinical significance is questionable.

IMA has been reported to increase as soon as the ischaemic insult starts and stays high, throughout the reversible cellular damage phase (Gaze 2009). Besides, IMA is an end product of an oxidative stress lacking tissue specificity (Gaze 2009) and proposed to be generated by hypoxia, acidosis, energy-dependent membrane disruption and exposure to free iron and copper (Bar-Or et al. 2000; Roy et al. 2006; Sbarouni et al. 2011). Therefore, it has reported to be affected by the albumin, lactate and blood glucose levels (Domínguez-Rodriguez and Abreu-Gonzalez 2010). Strenuous physical exercise, tourniquet application during surgery and arterial clamping during revascularisation procedures are the previously reported clinical conditions correlated with increased IMA levels (Apple et al. 2002; Refaai et al. 2006). Likewise, a partial or intermittent obstruction of umbilical blood flow in an intrauterine period might be associated with elevated IMA levels. But, there is no certain data about this issue. From this aspect, in our study, an intrauterine nuchal cord seems not to end up with a foetal tissue ischaemia reflected by IMA levels, before the initiation of the labour.

Depending on population-based studies, the routine screening for nuchal cord is not recommended (Clapp et al. 2003; Mastrobattista et al. 2005; Sheiner et al. 2006). In addition, an early detection might lead to unnecessary anxiety in patients and the healthcare professionals (Sherer and Manning 1999).
Also, the detection of nuchal cord is not an absolute medical indication for a C-section on its own (National Collaborating Centre for Women’s and Children's Health (UK) 2011). However, with increasing concern about the medico-legal issues in obstetrics, a shift from the more severe to the milder and wider indications for C-section has appeared (Gao et al. 2013). Reports from different regions of the world claim that, the rate of C-section associated with the nuchal cord ranges between 11.1 and 35% (Sheiner et al. 2006; Onderoglu et al. 2008; Nkwabong and Fomulu 2011) being one of the common indications for a caesarean delivery for perceived safety reasons (Nkwabong and Fomulu 2011). The factors associated with adverse neonatal outcomes correlated with a nuchal cord are the tightness of the cord (had to be cut for the progression of delivery), the number of loops and the time of persistence of nuchal cord (Clapp et al. 1999).

Even if the lack of data about the tightness of the loops and the time of persistence of nuchal cord are the limitations of this study, detection of these parameters is almost impossible in routine practice. Another limitation of the study might be the absence of the data regarding albumin levels in the maternal and cord blood samples since the albumin level is one of the mostly known interfering factors with the IMA levels. This is because IMA is a fraction of the albumin affected by ischaemia, its levels have been shown to be negatively correlated with the albumin levels when it is in normal range (10–49 g/L) but should be evaluated cautiously when the albumin levels are extremely low (< 3.4 g/L) (Gaze et al. 2006; Lippi et al. 2007; Gafsou et al. 2010; D’souza et al. 2014).

In conclusion, this study indicates that, a nuchal cord has an impact on the foetal cord blood gas parameters to some degree before the initiation of the labour process. Fortunately, this impact does not end up with foetal tissue ischaemia which was evaluated by the cord blood IMA levels. As this is the first study concerning this issue, further studies are needed to relieve the ‘anxiety of the obstetricians’ (Narang et al. 2014) and decrease the unnecessary interventions undertaken before the active stages of labour.

Disclosure statement

The authors report no conflicts of interest.

References


