Research Article

Cord Blood Ischemia-Modified Albumin Levels in Normal and Intrauterine Growth Restricted Pregnancies

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1. INTRODUCTION

Ischemia-modified albumin (IMA) is a relatively new biomarker in the identification of myocardial ischemia in advance or in the absence of myocardial necrosis [1]. Since IMA can be detected before troponin (a well-known marker of necrosis) and has a high sensitivity (82%) compared to traditional diagnostic tools (ECG-45%, troponin-20%), it is valuable for the diagnosis of myocardial ischemia in patients presenting with chest pain at the emergency department [1–3]. It is well known that IMA rises within minutes from the onset of the ischemic event and remains elevated for several hours after cessation of ischemia [2, 3].

The pathophysiological events of ischemia, including hypoxia, acidosis, and free radical generation, result in a conformational change of the N-terminus of albumin, leading to a reduction in its binding with the transition metals copper, nickel, and cobalt [4, 5]. The resulting molecule, IMA and its reduced binding of cobalt, has been exploited to produce a rapid automated test, the albumin cobalt binding assay [6].

Intrauterine growth restriction (IUGR) caused by chronic malnutrition and hypoxia, (consequent to deficient placental transport of nutrients and oxygen—asymmetrical pattern of IUGR)—is characterized by blood flow redistribution to vital organs (brain, myocardium, and adrenal glands), while other organs are deprived from sufficient blood flow [7–9]. This phenomenon called “the brain sparing effect” is usually accompanied by oligohydramnios [10, 11].

Taking into account “the brain sparing effect,” this study was based on the hypothesis that cord blood IMA levels should not differ between IUGR and appropriate-for-gestational-age (AGA) full-term pregnancies. Therefore, we aimed to investigate cord blood IMA levels in IUGR and AGA pregnancies at birth and correlate determined levels with gestational age, gender, and mode of delivery.

2. SUBJECTS AND METHODS

The Ethics Committee of our teaching hospital approved the study protocol. All included mothers provided signed informed consent before recruitment. In the time period from January 2006 to January 2007, one hundred and sixty
after clotting. The supernatant serum was stored at −80°C until assay.

IMA was measured with the albumin cobalt binding (ACB) test (inverness medical professional diagnostics, Bedford, UK). A cobalt solution is first added to serum, followed by addition of dithiothreitol (DTT). DTT reacts with the cobalt to form a colour that is measured by absorbance read spectrophotometrically. In serum of normal patients, cobalt binds to the N-terminus of albumin, which leaves little cobalt to react with DTT, producing a lighter colour. Conversely, in serum of ischaemic patients, cobalt does not bind to the N-terminus of IMA, which leaves more free cobalt to react with DTT, forming a darker colour. The ACB test is configured to run on Roche Cobas Integra 800 instrument. The minimum detectable concentrations, intra- and inter-assay coefficients of variation were 28 U/ml, 1.7% and 5.7%, respectively.

3. STATISTICAL ANALYSIS

Data regarding IMA were normally distributed (Kolmogorov Smirnov test). Linear regression analysis was used to examine the effect of gender, mode of delivery, parity, birth-weight, and gestational age on IMA levels. Student’s t-test was used to detect differences in continuous variables (IMA, birthweight, gestational age) between IUGR and AGA groups. Mann Whitney U test was used to detect differences in customized centiles between groups, since data regarding customized centiles were not normally distributed. Pearson’s chi square test was used to detect differences concerning gender, mode of delivery and parity between groups. Spearman’s or Pearson’s correlation coefficient were used to detect any positive or negative correlations. \( P < .05 \) was considered statistically significant. The power calculation of the study was 85%.

4. RESULTS

Doppler studies were performed in the IUGR group every 10–15 days, starting from the 32nd gestational week. During each Doppler velocimetry evaluation study, three consecutive measurements of the pulsatility index (PI) of the studied vessel were done and the mean value was recorded. Concerning uterine and umbilical arteries \([15, 16] ,\) mean PI values were progressively found to be in the upper physiological limits for the corresponding gestational age in 38 cases (ranging between the 90th and the 95th percentile), while in the
remaining 19 cases PI values showed increased impedance to flow, being above the 95th percentile for gestational age. Regarding middle cerebral arteries [17], Doppler studies showed resistance to be in the lower physiological limits for gestational age, indicating the initiation of blood flow redistribution process. Determined mean [95% confidence intervals (CI)] values of cord blood IMA levels were in the AGA group 112.44 (109.95–114.92) and in the IUGR group 115.54 (111.97–119.12). No significant differences in cord blood IMA levels were found between IUGR cases and AGA controls. In both groups, cord blood IMA levels were significantly elevated in cases of caesarean section (by 4.676 IU/mL on average) compared to cases of vaginal delivery ($b = 4.676$, CI 95%: 0.328–9.025, $P = .035$). Additionally, cord blood IMA levels were significantly increased (by 5.012 IU/mL on average) in cases of multigravidas compared to primigravidas ($b = 5.072$, CI 95%: 0.768–9.256, $P = .021$). Finally, cord blood IMA levels did not depend on gestational age or gender.

5. DISCUSSION

It has been recently reported that IMA is a highly sensitive biomarker, reflecting the myocardial ischemic condition prior to progression to myocardial necrosis [18–20]. In this respect, IMA has been reported to increase after percutaneous coronary interventions and in acute coronary syndromes [1, 21]. In this setting, elevated IMA levels may result from increased oxidative stress, caused by ischemia reperfusion injury or other mechanisms linked to primary reduction of coronary blood flow or muscle damage [1, 21–23].

Although there is a growing body of evidence regarding IMA in the area of monitoring acute coronary syndromes in adults [1, 18–23], data concerning the perinatal period are sparse [24, 25]. In this respect, higher cord blood IMA values were documented in complicated deliveries, indicating fetal distress and/or hypoxia [24]. Furthermore, elevated maternal serum IMA levels have been recently demonstrated in early normal pregnancy, supporting the hypothesis that normal trophoblast development is associated with a hypoxic intrauterine environment [25].

In line with our hypothesis, the results of the present study indicate a lack of significant differences in cord blood IMA levels between nondistressed IUGR cases and AGA controls, suggesting no evidence of myocardial damage in the former, possibly due to sparing of vital organs (e.g., brain, heart) [7–9]. Similarly, previous studies of ours reported that circulating levels of neurotrophins, which are important for pre- and postnatal brain development, as well as of cardiac troponin-I, which is a highly specific indicator of myocardial damage, did not differ between asymmetric nondistressed IUGR and AGA groups [26, 27].

On the other hand, contrary to our expectations, cord blood IMA levels were significantly elevated in cases of elective caesarean section compared to cases of vaginal delivery. In the literature, no evidence exists whether the fetus is subject to oxidative stress during labour [28]. Several studies have shown that umbilical arterial blood of newborns delivered vaginally or after emergent caesarean section contains higher levels of oxidation products than the blood of newborns delivered by elective caesarean section [29–32]. However, other reports suggest that oxidative stress in the fetal circulation does not depend on the mode of delivery [28]. In fact, a recent study even found that the “reservoir” of antioxidants in the fetal red blood cell compartment is higher in infants delivered vaginally than in those delivered by elective caesarean section [33]. It should be noted that all neonates included in our study were born healthy, as evaluated by Apgar scores and pH values.

Moreover, in our cohort, cord blood IMA levels were found to depend on parity, being significantly elevated in offspring of multigravidas. Relatively, epidemiological studies have demonstrated a consistent relationship between the number of pregnancies and the subsequent development of cardiovascular disease, due to an increase in oxidative damage during late pregnancy [34, 35]. The association, found between cord blood IMA levels at term and parity in the present study, may have important implications in the development of atherosclerosis and long-term cardiovascular health of women of high parity [34, 35].

In conclusion, cord blood IMA levels at term do not differ between IUGR cases and AGA controls, possibly due to the sparing of vital organs, like the heart. Furthermore, higher oxidative stress may account for the elevated cord blood IMA levels in cases of elective caesarean section, as well as in the offspring of multigravidas. Oxidative stress indicated by elevated IMA levels in women of high parity may have important implications in their long-term cardiovascular health and warrants further investigation.

REFERENCES


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