European Journal of Obstetrics & Gynecology and Reproductive Biology 210 (2017) 182–188

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Review article

Ischemia modified albumin in perinatology

Aslı Yarcı Gursoy[a,*], Gamze S. Caglar[a], Selda Demirtas[b]

[a] Ufuk University Faculty of Medicine, Obstetrics and Gynecology Department, Ankara, Turkey
[b] Ufuk University Faculty of Medicine, Biochemistry Department, Ankara, Turkey

ARTICLE INFO

Article history:
Received 6 April 2016
Received in revised form 20 October 2016
Accepted 19 December 2016
Available online xxx

Keywords:
Ischemia modified albumin
Perinatology

ABSTRACT

Ischemia modified albumin is a novel marker of ischemia generated due to hypooxygenation and increased hydroxyl free radicals in low pH. The molecule has been licenced for clinical use as an early marker for acute coronary syndrome in cardiology. Since presence of ischemia might have serious and sometimes devastating effects in perinatology, various researches have evaluated its value in different clinical conditions. This narrative review aims to summarize the literature concerning the value of IMA in perinatology and guide for further research.

Contents

Introduction . . . 2
Assay principles of IMA . . . 2
Sampling and storage . . . 2
Albumin, the prominent factor affecting IMA levels . . . 2
Maternal levels of IMA . . . 2
IMA levels in non-complicated pregnancy . . . 2
IMA levels in complicated pregnancies . . . 4
Early pregnancy loss . . . 4
Recurrent pregnancy loss . . . 4
Gestational diabetes mellitus . . . 4
Mothers bearing small-for-gestational-age (SGA) fetuses . . . 4
Preeclampsia . . . 5
Route of anesthesia at delivery . . . 5
Umbilical cord levels of IMA . . . 5
Non- complicated pregnancies . . . 5
Route of delivery and anesthesia . . . 5
The demographic factors effecting IMA levels in uncomplicated pregnancies . . . 5
Complicated pregnancies . . . 5
Gestational diabetes mellitus . . . 5
Intrauterine growth restriction . . . 5
Complicated delivery . . . 6
Neonatal complications . . . 6
Conclusions . . . 6
Conflict of interest . . . 6
Condensation . . . 6
References . . . 6

* Corresponding author at: Ufuk University Faculty of Medicine, Department of Obstetrics and Gynecology, Mevlana Bulvarı (Konya Yolu), No:86–88, 06520 Balgat/Ankara, Turkey.
E-mail address: asliyarci@gmail.com (A. Yarcı Gursoy).

http://dx.doi.org/10.1016/j.ejogrb.2016.12.022
0301-2115/

Introduction

Albumin is the most abundant protein in human plasma, which acts as a buffering agent for toxic molecules. The N-terminus of albumin molecule binds metals, in addition to nucleic acid, lipids and other proteins. The structure of albumin molecule is altered gradually in the presence of ischemia. The cascade starts with hypo-oxygenation accompanied by lowered pH. When hydroxyl free radicals are generated, the N-terminus of albumin molecule is damaged. Altered albumin is unable to bind divalent metals and release the bound forms [1] called ischemia modified albumin (IMA) [2].

The molecule is mostly studied in cardiologic events, elevated before necrosis, at early stages of ischemia. IMA is proposed to be an efficient endogenous response to ischemia, preventing myocardial damage or limiting the extent of myocyte necrosis [3]. IMA is approved by US Food and Drug Administration (US FDA) for use as an early marker in ruling out acute coronary syndrome in low-risk patients by the Albumin Cobalt Binding (ACB) assay [3]. But also, IMA levels have been shown to increase in pathological conditions other than myocardial ischemia such as pulmonary embolism [4], poor glycemic control in Type II diabetes mellitus [5], trauma [6], acute decompensated heart failure [7] and acute blood loss induced ischemia [8]. On the other hand, IMA levels have been shown to decrease in clinical conditions with increased lactate concentrations such as sepsis, muscle ischemia and renal failure [9,10]. Accumulating evidence indicating IMA as a valuable marker of ischemia, boost interest for researchers in perinatology (Table 1). This review summarizes the results of the electronic research performed in PubMed, Scopus, and Google Scholar. All databases were assessed up to April 2016. The databases were searched for key words ‘ischemia modified albumin AND maternal OR fetal OR cord blood OR preeclampsia OR intrauterine growth retardation OR gestational diabetes OR abortion OR pregnancy loss OR anesthesia OR delivery OR neonate OR pregnancy’ concerning the value of levels in every aspect of perinatology.

Assay principles of IMA

The principle for measuring IMA levels relies on the modification of the albumin at the presence of oxygen radicals [11,12]. In normal conditions, cobalt is bound to albumin with minimal circulating free levels [1]. But modified albumin due to radicals, is unable to bind cobalt and unbound amount of cobalt enables measurement of IMA levels indirectly. The reactant used for measurement of free cobalt levels is, dithiothreitol, which results in development of colour in a spectrum ranging between 470 and 500 nm [2]. There are two tests available, one of which is manual [13] and the other automated commercial assay (Cobas Fara®/ Albumin Cobalt Binding® Test and Roche Cobas Mira® Plus) [13,14]. The manual assay gives the measurements in absorbance units (A.U., ABSU) while the commercial assay gives the results in arbitrary units (kUI^{-1}) [2]. Other than these, quantitative sandwich enzyme immunoassay technique (ELISA) is another but rarely used method [15].

Sampling and storage

Serum rather than plasma sample should be used. The serum sample should be drawn into a non-heparinized closed tube, centrifuged within 1 h, and stored at +4C° before running to instrument [16]. The duration of time from blood withdrawal to instrument result must be less than 5 h [16]. In case of storage for longer durations, the specimens should be kept at −20 °C and thawed at +4 °C [16]. The storage of blood specimens at 26 °C or centrifugation just prior to the analysis, result with decreased IMA values measured with ACB assay. Also, the test reagents should be kept in refrigerator (+4 °C) and are known to be stable for 12 days after reagent two (DTT concentrate) reconstitution [16].

Albumin, the prominent factor affecting IMA levels

For more accurate results, total albumin levels should be between 3 and 5.5 g/dL. The albumin concentration of the sample might effect ACB assay results in opposite direction [1,11]. Especially in cases with low albumin levels (<3.5 g/dL) the change in IMA results is stronger [1]. This determination especially gains importance while working on special populations such as newborns and pregnant women whose normal albumin value ranges are lower than normal adult population[17,18]. In the samples with albumin levels ranging between 0 and 6 g/dL, IMA values changed up to 37–48% from the baseline with each 1 g/dL alteration of albumin [11]. The negative correlation between albumin and IMA levels has led to generation of adjustment formulas for interference on serum IMA assay. The formula suggested by Lee et al. [19] is “albumin-adjusted IMA index”, defined as: serum albumin concentration (g/dL) × 23 + IMA (U/mL)–100. Another formula is based on median albumin levels of the target population as: (individual serum albumin concentration/median albumin concentration of the population) × IMA [20] (Lippi et al.). Others [21] suggested IMA/Albumin ratio for altered albumin levels.

Maternal levels of IMA

IMA levels in non-complicated pregnancy

The impact of pregnancy on IMA levels have been evaluated in three prospective studies. The first report was held in 2007 by Prefumo et al. [22]. First trimester levels of IMA in 66 singleton pregnancies at 11–13th weeks of gestation were compared with 26 non-pregnant controls [22]. The median IMA level in the pregnant group (115.14 kU/L) was significantly higher ($p < 0.001$) than in non-pregnant controls (73.71 kU/l). The authors suggested pregnancy as the first physiological condition with supraphysiological IMA levels [22]. Others [15] also reported significantly higher IMA levels in healthy pregnant subjects compared to non-pregnant controls (median values: 173.2 vs 118.8 ng/mL, respectively, $p < 0.05$). The first explanation for high IMA levels in pregnant women might be the hypoxic intrauterine environment associated with early human placentation due to plugging of spiral arteries by extra villous trophoblast cells [23]. Secondly, the increased levels of IMA in the late first trimester might be a result of radical oxygen species increased due to rise in oxygen concentrations induced by maternal blood circulation in the intervillous space [24]. Therefore, the high IMA levels in first trimester might be a compensatory outcome for neutralization of oxidative stress rather than a result of it.

On the contrary, another study [25] about IMA reported mean levels of 0.46 ± 0.12 ABSU in the first trimester (<14 weeks, n = 24), 0.58 ± 0.11 ABSU in the second trimester (14–28 weeks, n = 34) and 0.61 ± 0.11 ABSU in the third trimester (>28 weeks, n = 35). This study documented gradually increasing IMA levels throughout pregnancy which is still lower than controls (n = 23, 0.67 ± 0.08 ABSU) ($p = 0.001$). The limitation of this study was sampling which might decrease the reliability of the results.

The reference values for IMA levels in pregnancy still needs to be validated in further large population based studies. But until then, the results from the first study reported by Prefumo et al. cannot be disregarded [22]. As previously mentioned, FDA approved IMA for diagnosis of myocardial ischemia with determined cut off values of >95 kU/L with ACB assay. However, the study by Prefumo et al. [22], reported higher IMA levels in 84% of