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Short communication

The association between ischemia modified albumin and placental histopathology in uncomplicated term deliveries

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ABSTRACT

Ischemia modified albumin (IMA) is a marker of ischemia elevated in different clinical conditions and its use for hypoxia in perinatology is of current interest. We aimed to investigate the association between maternal and cord blood IMA levels and placental histopathological findings in uncomplicated term deliveries. In this study, placental histopathological evaluation in uncomplicated deliveries that ended with healthy newborns revealed 80.6% vasculopathy. The results support the hypothesis that hypoxia exceeding the placental reserve ends with fetal compromise. Moreover, the presence of maternal vasculopathy in placenta is not correlated with maternal and fetal IMA levels.

1. Introduction

Ischemia modified albumin (IMA) generation occurs via superoxide free radicals in ischemia [1]. IMA lacks tissue specificity and increases 5–10 min after the ischemic event; it stays in the serum for 30 min unless ischemia persists [2]. Although IMA has been more commonly studied as a marker of ischemia in acute coronary syndrome [3], elevations in serum IMA levels have been observed in a variety of clinical conditions [4,5]. The value of IMA as a marker of hypoxia in perinatology is of current interest. A normal pregnancy is characterized by a significant maternal adaptive response and the production of many pro-oxidant and vasoactive substances by the placenta. IMA levels become significantly elevated as pregnancy progresses, suggesting a physiologic oxidative stress that increases gradually [6]. Moreover, maternal levels of IMA early in pregnancies are higher in defective placental development associated with future preeclampsia, recurrent pregnancy losses during the first trimester and fetal growth restriction [7–9].

Reduced blood flow to the fetus causes insufficient oxygenation, anaerobic metabolism, acidosis and finally IMA generation. A complicated delivery causes an almost 50% increase in fetal cord blood IMA levels compared with normal deliveries [10]. Acute or chronic decreased oxygen content may cause placental and fetal hypoxia [11]. Since the oxygen consumption of the placenta is four times higher than that of the fetus, 'in utero hypoxia' affects the placenta first and then the fetus. Unless hypoxia exceeds the placental reserve, the fetus not compromised [12]. In this study, we evaluate the association between maternal/fetal IMA levels and placental histopathological findings in uncomplicated term deliveries with apparently healthy fetuses.

2. Methods

We recruited 36 pregnant women delivering appropriately for gestational-age fetuses [13] via cesarean section electively between 37 and 42 weeks of gestation. Institutional Ethics Committee approval and written informed consent was obtained from all of the participants. The exclusion criteria included complicated pregnancies (e.g., fetal growth restriction, gestational diabetes mellitus, preeclampsia, fetal congenital anomaly, oligohidroamnios, plasenta previa), mothers with chronic illnesses (e.g., hypertension, diabetes mellitus) and any history of cardiac symptoms, angina, myocardial infarction, coronary artery disease,

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Table 1
Clinical characteristics of pregnancies for placentas studied.

Parameter				
Gravidity	Median = 1	25–75% = 1–2	Range = 1–8	
Parity	Median = 0	25–75% = 0–1	Range = 0–2	
Gestational age (weeks)	Mean = 38.5	SD = 0.7	Range = 37–40	
Maternal age (years)	Mean = 30.5	SD = 4.8	Range = 22–42	
Race	Black n = 0	White n = 36		
Prenatal Medications	Iron n = 36	Other (multivitamin) n = 36		
Antibiotics in labor	None, n = 0	Penicillin, n = 36		
Beta strep status	Positive	Negative	Unknown n = 36	
Anesthesia	Epidural, n = 36	General, n = 0	Narcotics, n = 0	
Cervical ripening agent	Prostaglandins, n = 0	None, n = 36		
Delivery mode	C-section, repeat, no labor: n = 18	C-section, repeat, with labor: n = 0	C-section, primary, no labor: n = 18	C-section, primary, with labor: n = 0
Maternal oxygen given at delivery?	Yes, n = 36	No	Unknown	
Birth weight (grams)	Mean = 3382.85	SD = 457.95		
Placental weight (grams)	Mean = 628.82	SD = 146.41		
Baby's sex	Female = 17	Male = 19		

vascular disease, inflammatory disease, smoking, alcohol consumption, abnormal albumin levels, or multiple pregnancies. Regional anesthesia was given to all women. Maternal blood samples before any intervention and cord blood immediately after the delivery were collected for IMA analysis. We also performed umbilical cord acid base analyses. We analyzed the IMA concentrations via a cobalt binding test in absorbance units (ABSU) (coefficient of variation of 3.5%). The placental weights for the gestational weeks were recorded [14], and the same pathologist (E.A.) blindly analyzed the specimens according to Turowski category 4 [15].

3. Results

The demographic characteristics are summarized in Table 1. All babies had Apgar scores ≥8 at the 1st and 5th minute. None of the newborns had chromosomal abnormalities or required neonatal care unit admission. None of the fetuses had fetal acidosis (pH < 7.0). The mean pH value of the umbilical cord was 7.33 ± 0.05, the mean PCO_2 was 47.91 ± 6.96 and the mean PO_2 was 17.60 ± 6.35. The histopathological findings are summarized in Table 2. Twenty-nine patients (80.6%) had pathologies showing maternal vasculopathy. None of the placentas revealed intervillous thrombi or abruptio markers. The mean maternal and fetal IMA levels were 1.02 ± 0.27 and 1.12 ± 0.64 ABSU, respectively. Maternal and fetal IMA levels were not correlated with either the histopathological findings or with the characteristics of the mothers (age, gravidity, parity, and gestational age) ($p > 0.05$). Placental weight was positively correlated with fetal weight ($r = 0.663$; $p < 0.001$).

4. Discussion

Maternal and fetal IMA levels were not correlated with placental histomorphological changes in uncomplicated pregnancies. The placenta responds to hypoxia in various ways that need to be explained in a clinical context [11]. The real diagnostic significance of many hypoxic-ishemic placental lesions has not been firmly defined [12]. According to the results of this study, despite decidual vasculopathy in 80% of the placenta samples, none of the fetuses exhibited fetal compromise indicative of placental capacity. Furthermore, the lack of a correlation of these findings with umbilical cord IMA levels supports that assertion that the placenta has a high capacity for protecting the fetus. Moreover, Turowski et al. investigated placental histomorphologies in 315 intrauterine fetal deaths and 31 healthy newborns [15]. The incidence of placental findings of decidual vasculopathy was 75% in cases of fetal demise; it was 74% in healthy newborns [15]. These results suggest that abnormal placental histopathologies occur irrespective of fetal compromise.

Up until now, IMA has been used largely in complicated pregnancies to detect increased oxidative stress and ischemia either in the mother or the fetus [16,17]. Other than being a diagnostic marker of ischemia, the IMA levels of mothers have been investigated as a potential predictive marker for fetal well being. After maternal perception of reduced fetal movements, the predictive value of maternal IMA levels on fetal well-being was examined by Dutton et al. [18]. Since reduced fetal movement is linked to a clinical manifestation of the fetus reacting to nutrient and oxygen deprivation secondary to placental insufficiency [19], placental molecular analyses were also performed. The authors found that maternal IMA levels and placental expression of hormones were similar in cases with poor and normal outcomes [18]. These results of Dutton et al. support our findings, indicating that placental markers are not associated with maternal levels of IMA. However, additional studies to evaluate fetal IMA levels in acute and chronic hypoxia with diffuse and focal placental lesions are required.

Although a clinically oriented, unifying and simple placental classification system [15] was used in this study for histopathological analyses of the placenta samples, there are no universally agreed criteria as to what constitutes a clinically significant histological lesion of the placenta in an uncomplicated pregnancy [20]. Moreover, a clinically applicable novel test to detect placental function and the associated fetal response is needed. Finally, the small number of placental samples is a limiting factor in this preliminary study. However, our results contribute to the clinical value of IMA in perinatology.

Table 2
Abnormal histopathological findings of placental specimens.

	n	(%)
Placenta percentile (<10%)	2	5.6
Increased intervillous fibrin (%30–50)	9	25
Distal villous hypoplasia	3	8.3
Acute cotyledon infarct	25	69.4
Subacute cotyledon infarct	8	22.2
Chronic cotyledon infarct	7	9.4
Chorangiosis	14	38.9

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