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Ischemia-modified albumin levels in threatened abortion and missed abortion compared to healthy pregnancies

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Abstract

This study aims to investigate differences in serum ischemia-modified albumin (IMA) and adjusted IMA levels among cases of healthy intrauterin pregnancies, threatened abortions, and missed abortions. In this prospective case-control study, a total of 90 participants were included, distributed into three groups: missed abortion (n = 30), threatened abortion (n = 30), and intrauterin healthy pregnancy (n = 30). IMA and adjusted IMA values were calculated for each group. Our findings revealed no significant differences in serum IMA and adjusted IMA concentrations among the three groups. Additionally, there were no correlation observed between IMA levels, adjusted IMA levels, and maternal age, body mass index (BMI), white blood cell (WBC) count, neutrophil count, lymphocyte count, platelet count, neutrophil-to-lymphocyte ratio (NLR), platelet-to lymphocyte ratio (PLR), mean corpuscular volume (MCV), and red cell distribution width (RDW). The study concludes that IMA lacks a reliable capacity to differentiate between potential healthy intrauterine pregnancies, threatened abortions, or missed abortions during the first trimester. These results highlight the need for exploring alternative biomarkers that may offer greater specificity in distinguishing various pregnancy outcomes in early gestation.

Keywords: ischemia-modified albumin, healthy pregnancy, threatened abortion, missed abortion, early pregnancy

1. Introduction

Early pregnancy loss (EPL), also referred to as early miscarriage, represents the most common form of pregnancy termination, usually occurring during the first trimester of gestation (1). Vaginal bleeding and uterine cramps are common symptoms of pregnancy loss that can occur in normal, ectopic, and molar pregnancies, causing distress for patients and uncertainty for healthcare practitioners. Early pregnancy loss is the most common problem during the initial stages of pregnancy. Determining the true frequency of pregnancy loss is challenging due to the occurrence of multiple losses before clinical detection of pregnancy. Estimates of EPL incidence, derived from logistic regression models, have reached figures as high as 31%, although this incidence declines to approximately 10% when considering losses occurring in clinically recognized pregnancies during the first trimester (2,3).

Pregnancy loss can occur either after implantation but before clinical recognition or after clinical recognition, which is determined by a clinician or conventional pregnancy testing (3). However, according to established medical standards, the failure of a fertilized egg to implant is not considered pregnancy. The pathogenesis of early miscarriage is not yet clear (4). Typical causes of pregnancy loss at any stage include chromosomal disorders, maternal anatomic defects, and trauma. Potential causes linked to pregnancy loss include advanced maternal age, medical issues, use of medicine or substances, and exposure to environmental factors (5). Implantation disorders can result in a more ischemic environment, contribute to oxidative stress and defective insertion in early pregnancy, and potentially result in early pregnancy loss. Although various biomarkers have been defined for early diagnosis, diagnostic tools such as ultrasonography and serum β-HCG detection are inadequate at the first examination in 8-31% of cases (6,7). Therefore, it is still one of the most important causes of pregnancy-related maternal morbidity and mortality and better markers are needed.

The N-terminal region of the albumin molecule, responsible for binding divalent heavy metals like nickel, copper, and cobalt, undergoes structural changes due to

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hydroxyl radicals produced during acidosis and hypo-oxygenation resulting from ischemia. Consequently, it loses its ability to bind divalent heavy metals. This altered form of albumin is referred to as ischemia-modified albumin (IMA). (8). During pregnancy, an elevation in oxidative stress, attributed to hypoxia/reperfusion, is observed due to vascular transformations and perfusion adaptations supporting the materno-fetal area. Some past studies have shown that IMA levels in the first trimester of pregnancy are higher than in women who are not pregnant (9,10). Moreover, it has been noted that IMA levels are elevated in pregnancies complicated by conditions such as preeclampsia, fetal growth restriction, preterm labor, and gestational diabetes mellitus when compared to healthy pregnancies (11–14). Early pregnancy loss in the first trimester has been identified as a factor leading to oxidative stress, much like other reproductive challenges such as preeclampsia, fetal growth restriction, and preterm labor (15,16). Therefore, in this study, we aimed to compare IMA and adjusted IMA levels in healthy pregnancies, threatened abortion and missed abortion.

2. Materials and Methods

This prospective case-control study was carried out in a tertiary obstetric care center, in Ankara, Turkey, between August 2023 and November 2023. All participants provided written informed consent. The study included a population of 90 women in the first trimester of pregnancy admitted to our tertiary center for standardization. We classified the patients into three groups: those with an intrauterine healthy pregnancy (n = 30), those with a threatened abortion (n = 30), and those who aborted or were admitted for dilation and curettage because fetal heart activity was not detected (n = 30).

Participants with a history of ischemic disease, diabetes, heart disease, hypertension, thyroid disease or other known medical conditions, smokers, and multiple pregnancies were excluded from the study.

2.1. Sample collection

Maternal blood samples, totaling 5 milliliters per participant, were collected in heparinized tubes for IMA analysis. These samples were first centrifuged at 4000 g for 10 minutes. The serum obtained after centrifugation was stored at -80 degrees Celsius until analysis. Serum IMA levels were assessed using a colorimetric assay method outlined by Bar-Or et al. (17). This method relies on albumin's biochemical capability to bind external cobalt. In this process, 200 µL of subject serum was mixed with 50 µL of 0.1% cobalt II chloride ($CoCl_2$, $6H_2O$), followed by a 10-min incubation in the dark and at 37°C to facilitate cobalt-albumin binding. Then, 50 µL of dithiothreitol (DTT) was added as dye. Following a 2-minute incubation, 1 mL of 0.9% sodium chloride (NaCI) solution was added to diminish the binding capacity. The blank was prepared in the same manner using distilled water instead of DTT. Absorbance at 470 nm was measured using a UV-visible spectrophotometer (Jenway 6315, Staffordshire, United Kingdom). IMA values were measured and reported in absorbance units (ABSUs). Each sample underwent two measurements, and the average value was recorded. Adjusted IMA levels were computed using the formula proposed by Lippi et al. (18): (serum albumin concentration/median albumin concentration of the study population) x patient's IMA value.

2.2. Statistical analysis

The data analysis utilized version 26.0 of the Statistical Package for the Social Sciences (IBM Corporation, New York, US), with a predetermined significance level of $p < 0.05$ for all conducted analyses. The data were shown as mean±standard deviation (SD), median (min-max) and n,(%) in accordance with their characteristics. The comparison of categorical variables between groups employed the chi-square test, while analysis of variance (ANOVA) was applied for multiple comparisons of continuous variables. If a substantial difference was found during the study, a homogeneity of variances assessment was conducted to pinpoint the particular groups showing discrepancies. If the variances were distributed homogeneously, the Scheffe test was used as a post hoc test. If the variances were determined to be heterogeneous, a different post hoc test, the Tamhane T2 test, was used. Spearman's correlation test was employed to assess the correlation between groups.

3. Results

The study included a total of 90 women, comprising 30 pregnant women diagnosed with threatened abortion, 30 with missed abortion, and 30 healthy pregnant women. At measurement, no statistically significant differences were observed in patients' ages, body mass index, or gestational age. However, significant statistical differences were noted among the groups (intrauterine pregnancy vs threatened abortion and intrauterine pregnancy vs missed abortion) with respect to parity ($p<0.001$). (Table 1).

Table 2 presents the laboratory parameters and serum IMA levels of the participants. There was no statistically significant difference between the groups in terms of serum white blood cell (WBC) count, hemoglobin (Hb) level, hematocrit (Hct) level, neutrophil count, lymphocyte count, platelet count and red cell distribution width (RDW). Similarly, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), maternal serum IMA, adjusted IMA, total protein and albumin levels were statistically similar between groups. The values for mean corpuscular volume (MCV) and mean platelet volume (MPV) were noted to be elevated in the group of healthy pregnant women when compared to both the threatened abortion and missed abortion groups ($p=0.032$ and $p=0.001$, respectively). (Table 2).

Table 1. Maternal and demographic characteristics of the participants

	Intrauterine Pregnancy n= 30	Threatened Abortion n= 30	Missed Abortion n=30	p
Maternal age (year) (mean±SD)	29±5	26±6	26±5	0.135
BMI at during test (kg/m^2) (mean±SD)	24±4	24±4	25±5	0.369
Parity (n,%)				<0.001
Nulliparous	4 (13.3%)	21 (70%)	17 (56.7%)	
Multiparous	26 (86.7%)	9 (30%)	13 (43.3%)	
Gestational age at measurement (weeks) (mean±SD)	10.1±2.3	9.2±2.6	8.8±2.3	0.120

Table 2. Laboratory parameters and serum ischemia modified albumin levels of the participants

	Intrauterine Pregnancy n= 30	Threatened Abortion n= 30	Missed Abortion n=30	p
Ischemia modified albumin level in maternal blood (AbsU) (mean±SD)	0.700±0.015	0.700±0.014	0.696±0.015	0.391
Adjusted ischemia modified albumin level in maternal blood (AbsU) (mean±SD)	0.681±0.047	0.704±0.052	0.698±0.043	0.156
Albumin (g/dL) (mean±SD)	4.18±0.29	4.32±0.31	4.32±0.31	0.117
Total protein (g/dL) (mean±SD)	6.95±0.39	6.91±0.52	6.89±0.35	0.880
WBC (*10^3/mm^3) (mean±SD)	7.9±1.89	8.39±2.41	7.64±1.97	0.382
Hemoglobin (g/dL) (mean±SD)	12.64±0.99	12.7±1.39	12.31±0.88	0.351
Hematocrit (%) (mean±SD)	37.63±3.15	37.51±3.42	36.45±2.76	0.278
Neutrophil (*10^3/mm^3) (mean±SD)	5.52±1.83	6.1±2.06	5.22±1.69	0.186
Lymphocyte (*10^3/mm^3) (mean±SD)	1.61±0.48	1.7±0.64	1.79±0.54	0.457
Platelet (*10^3/mm^3) (mean±SD)	241±65.1	246.8 ±60.2	228.2±43.1	0.437
Neutrophil-to-lymphocyte ratio (mean±SD)	3.71±1.67	3.98±1.69	3.08±1.11	0.067
Platelet-to-lymphocyte ratio median (min-max)	156.8 (75.9-257.5)	163.3 (62.7-372.6)	126.3 (66.4-242.3)	0.248
MCV (fL) median (min-max)	86.7 (80.2-100.5)	84.6 (65.9-95.1)	83.5 (64-99.6)	0.032
RDW (%) median (min-max)	14.1 (13.3-17.5)	14.5 (12.2-19.3)	14.4 (12.2-22.4)	0.401
MPV (fL) median (min-max)	8.2 (6.9-10.8)	7.4 (6.5-9.2)	7.5 (6.7-9.4)	0.001

BMI: Body mass index, WBC: White blood cell, MCV: Mean corpuscular volume, RDW: Red cell distribution width, MPV: Mean platelet volume

The relationship between maternal ischemia-modified albumin levels and maternal-gestational parameters is shown in Table 3. A correlation was found between IMA levels, adjusted IMA levels and maternal age, BMI, WBC count, neutrophil count, lymphocyte count, platelet count, NLR, PLR, MCV, and RDW. While Hb level (r=-0.208, p=0.049) and Hct level (r=-0.233, p=0.027) exhibited negative correlations with IMA levels, adjusted IMA levels did not show a correlation. Moreover, gestational age at measurement (r=-0.533, p<0.001), albumin (r=0.946, p<0.001), total protein (r=0.631, p<0.001), MPV (r=-0.239, p=0.024), and adjusted IMA levels were correlated, but IMA levels did not demonstrate a correlation. (Table 3).

Table 3. Relationship between maternal ischemia modified albumin levels and maternal-gestational parameters

	Ischemia modified albumin (AbsU)		Adjusted ischemia modified albumin (AbsU)	
	r	p	r	p
Maternal age (year)	-0.141	0.186	-0.170	0.110
BMI at during test (kg/m^2)	0.049	0.647	-0.018	0.868
Gestational age at measurement (weeks)	0.029	0.785	-0.533	<0.001
Albumin (g/dL)	-0.166	0.118	0.946	<0.001
Total protein (g/dL)	-0.158	0.136	0.631	<0.001
WBC (*10^3/mm^3)	0.071	0.506	-0.087	0.417
Hemoglobin (g/dL)	-0.208	0.049	0.159	0.135
Hematocrit (%)	-0.233	0.027	0.116	0.278
Neutrophil (*10^3/mm^3)	-0.041	0.702	-0.110	0.301
Lymphocyte (*10^3/mm^3)	0.056	0.601	-0.060	0.574
Platelet (*10^3/mm^3)	0.130	0.221	0.127	0.235
Neutrophil-to-lymphocyte ratio	-0.074	0.489	0.019	0.862
Platelet-to-lymphocyte ratio	0.069	0.517	0.166	0.118
MCV (fL)	-0.097	0.365	-0.088	0.408
RDW (%)	0.036	0.737	-0.105	0.323
MPV (fL)	-0.135	0.205	-0.239	0.024

BMI: Body mass index, WBC: White blood cell, MCV: Mean corpuscular volume, RDW: Red cell distribution width, MPV: Mean platelet volume

4. Discussion

Our study aimed to assess early pregnancy viability during the first trimester by comparing serum IMA and adjusted IMA levels among women experiencing threatened abortion, missed abortion, and those with healthy intrauterine pregnancies. The principal finding of our study revealed no significant differences among the three groups concerning serum IMA and adjusted IMA concentrations (p>0.05, for all). Ozdemir et al. conducted a comparative analysis of intrauterine pregnancies, specifically contrasting those with a history of recurrent pregnancy loss and currently missed abortion. Their findings revealed elevated levels of both IMA and adjusted IMA in the group with a history of recurrent pregnancy loss and currently missed abortion (19). Cengiz et al. explored IMA levels in three distinct groups: healthy intrauterine pregnancy, missed abortion, and non-pregnant individuals (20). Their results demonstrated significantly higher IMA and adjusted IMA levels in the healthy pregnancy group compared to the non-pregnant group. Additionally, IMA and adjusted IMA levels were significantly higher in the missed abortion group than in the healthy intrauterine pregnancy group. Dogan et al. conducted a comparative analysis across three groups—healthy intrauterine pregnancy, ectopic pregnancy, and missed abortion—assessing IMA levels. Notably, no significant differences were detected between the groups, although it's worth mentioning that adjusted IMA was not calculated in this study (21). Our results are similar to Dogan et al. It's crucial to note that our study population differs from that of Ozdemir et al. and Cengiz et al., emphasizing the importance of considering population-specific factors when interpreting the results and implications of such investigations.

Various studies in the current literature investigate the relationship between age and IMA levels. Some of these studies overlap with our research and show no significant relationship between advancing age and IMA values (22,23). However, some studies claim the opposite (9,13). This apparent inconsistency may stem from the diverse factors under scrutiny in these studies. The characteristics of the patient and healthy population examined in each study are different, which may affect IMA levels and cause different results in terms of age-IMA relationship. Considering the assumption that IMA levels are affected by the pathological variables investigated in studies, randomized studies are needed to investigate the relationship between age and IMA, especially in the healthy population.

We did not observe a correlation between BMI and IMA levels, which stands in contrast to the findings reported by Piva et al. and Mehmetoglu et al. These studies suggested a relationship between IMA levels and obesity, with higher IMA levels identified in obese patients (24,25). On the other hand, Yigitbasi et al. did not find a significant relationship between BMI and IMA (26). It is important to note that the populations studied in our research, focusing on pregnant women and those in the other mentioned studies, differ, potentially contributing to variations in the results.

While the literature reports a relationship between IMA and inflammation markers in studies conducted on inflammatory or infectious populations (24,27,28), our investigation found no

significant association between serum IMA levels and other inflammatory indicators, including WBC, neutrophil count, lymphocyte count, NLR, and PLR. This discrepancy may be attributed to the association of IMA with advanced oxidation processes that typically occur in the inflammatory pathway. Our study was not conducted in patients with primary inflammation or infection. Therefore, inflammation parameters do not contribute additionally to oxidation in our population. Consequently, it is reasonable to assert that IMA levels may not correlate with inflammation parameters in populations where active inflammation is not observed.

There are limitations to this study. First, although the sample size of 90 participants was reasonable, larger groups may provide stronger information. Second, the study did not evaluate specific factors known to influence IMA levels, such as dietary habits and specific lifestyle factors. Consideration of these variables could enhance the depth of the investigation. Third, only pregnant women were included in our study, which may have affected our potential correlation statistics.

In conclusion, our study indicates that IMA does not exhibit a reliable capacity to differentiate between a potentially healthy intrauterine pregnancy, threatened abortion, or missed abortion during the first trimester. The lack of significant changes in serum IMA levels in the first-trimester pregnancy viability follow-up suggests that IMA may function as a relatively less affected biomarker by physiological changes associated with early pregnancy.

Conflict of interest

The authors declared no conflict of interest.

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Authors' contributions

Concept: B.D.Ç., Design: B.D.Ç., B.B., Data Collection or Processing: B.D.Ç., B.K., Analysis or Interpretation: B.D.Ç., B.B., Literature Search: B.D.Ç., B.B., B.K., Y.E.U., H.L.K., O.E. Writing: B.D.Ç., B.B., B.K., Y.E.U., H.L.K., O.E.

Ethical Statement

Ethical permission required for the study was obtained by Ankara Etlik City Hospital Ethics Committee (Approval number and date: AEŞH-EK1-2023-393 and 09/08/2023).

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