Evaluation of Maternal Serum Ischemia Modified Albumin in Ectopic Pregnancy

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ABSTRACT:

BACKGROUND:

An ectopic pregnancy is defined as the implantation of a pregnancy outside the normal uterine cavity. Serum ischemia-modified albumin (IMA) and adjusted IMA appear to be significantly increased during pathological pregnancies.

AIM OF THE STUDY:

To compare the level of IMA in ectopic and normal pregnancies, thus understanding the association between oxidative stress and the incidence of ectopic pregnancy.

METHODS:

A case-control study that included 80 women; 38 of them with ectopic pregnancy, and the other 42 were healthy pregnant women. Patients with systemic diseases, a history of smoking, the use of anti-inflammatory drugs and antioxidants were excluded from the study. Serum IMA was measured using enzyme-linked immunosorbent assay (ELISA) for all participants.

RESULTS:

Means of IMA and adjusted IMA in women with ectopic pregnancy were significantly higher than that in women with normal pregnancy.

CONCLUSION:

There is an association between oxidative stress and ectopic pregnancy

KEYWORDS: Oxidative Stress, Antioxidant, Ischemia Modified Albumin, Ectopic Pregnancy.

INTRODUCTION:

An ectopic pregnancy (EP) is defined as the implantation of a pregnancy outside the normal uterine cavity. [(1)]

The first known description of an ectopic pregnancy is by Al-Zahrawi in the 11th century. [(2)]

The rate of ectopic pregnancy (EP) is 11 per 1000 pregnancies, with a maternal mortality of 0.2 per 1000 estimated EPs. About two thirds of these deaths are associated with substandard care. In recent decades, there have been significant advances in the diagnosis and management of EP. [(3)]

Nearly 95 percent of ectopic pregnancies are implanted in the various segments of the fallopian tube. The ampulla (70 %) is the most frequent site, followed by isthmic (12 %), fimbrial (11 %), and interstitial tubal pregnancies (2 %). [(4)]

The remaining 5 percent of non-tubal ectopic pregnancies implant in the ovary, peritoneal cavity, cervix, or prior cesarean scar. [(4)]

The pathogenesis of extrauterine pregnancy is of multifactorial origin. Up to half of all women with an extrauterine pregnancy have no recognized risk factors for it. (5) The postulated mechanisms include anatomical and/or functional tubal obstruction, impaired tubular motility and ciliary dysfunction, and molecular chemotactic factors that stimulate and promote tubal implantation. [(5)] A newly implicated factor in poor reproductive performance is oxidative stress, which describes an imbalance between antioxidant capacity and pro-oxidants. Reactive oxygen species (ROS) have at least an unpaired electron; due to this, they have a high reactive rate and interact comfortably with lipids, DNA, or protein and resulting in cellular and oxidation malfunction that may trigger pathological disorders. Oxidative stress has a significant influence on the span of the female reproductive life, and even on menopause. It is thought that the decline in fertility due to age may be

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modulated by oxidative stress. [6] It plays a vital role in pregnancy and parturition. [7,8] Lipid damage, Adenosine triphosphate (ATP) depletion, and inhibition of synthesis of protein are examples of mechanisms that exert pathological effects. [9] The literature on the effects of oxidative stress on female reproduction is ever increasing-concerning hydatidiform mole, [10,11] pre-eclampsia, [12,13] congenital disabilities induced by free radicals, (14) and other conditions such as abortions. [15]

The rise in oxidative stress may impact the tubal environment leading to a reduction in the tubal ciliary movement, which in turn retards the movement of the fertilized ovum. [16] Protection of the fertilized ovum from oxidative stress is determined to a large extent by the antioxidant status. [17]

Ectopic pregnancy presents as an either acute or chronic condition. Earlier patient presentation and precise diagnostic technology typically allow identification of acute conditions before rupture. [4]

In chronic cases, symptoms and signs of ectopic pregnancy are often subtle or even absent [4]. The classic triad is delayed menstruation, pain, and vaginal bleeding or spotting. [4] With tubal rupture, lower abdominal and pelvic pain is usually severe and frequently described as sharp, stabbing, or tearing. Abdominal palpation elicits tenderness. [4] Bimanual pelvic examination, especially cervical motion, causes exquisite pain. [4] The posterior vaginal fornix may bulge from blood in the rectouterine cul-de-sac, or a tender, boggy mass may be felt beside the uterus. Symptoms of diaphragmatic irritation develop in perhaps half of the women with sizable hemoperitoneum. Some degree of vaginal spotting or bleeding is reported by 60 to 80 percent of women with tubal pregnancy. [4] Although profuse vaginal bleeding suggests an incomplete abortion, such bleeding occasionally is seen with tubal gestations. Moreover, tubal pregnancy can lead to significant intraabdominal hemorrhage and hemorrhagic shock. In approximately half of women with a ruptured ectopic pregnancy, varying degrees of leukocytosis up to 30,000/μL may be documented. [4]

Several algorithms have been proposed to identify ectopic pregnancy. Most include these key components: physical findings, abdominal and transvaginal sonography (TVS), serial serum β-HCG level measurements and serum Progesterone level, and diagnostic surgery, which includes dilation and curettage (D&C), laparoscopy, and occasionally, laparotomy. [4]

Strategies that maximize the detection of ectopic pregnancy may result in the termination of normal intrauterine pregnancy (IUP). Conversely, those that reduce the potential for normal pregnancy interruption will delay ectopic pregnancy diagnosis.

The imaging technique used in the diagnosis of EP that includes abdominal, transvaginal, and color Doppler ultrasound has been reported to have a sensitivity of 90% and a specificity of 99.8%, with positive and negative predictive values 93% and 99.8%, respectively. [18]

Several biomarkers have been identified to permit the early diagnosis of ectopic pregnancy, including CA 125, pregnancy-associated plasma protein-A (PAPP-A), serum vascular endothelial growth factor (VEGF), and serum creatine kinase (CK). However, the results were conflicting, and most of them could not be used clinically. [19-22]

Ischemia Modified Albumin (IMA), which reflects the oxidative stress, may associate with the ectopic pregnancy. [23] This is because the development of pregnancy and placentation usually takes place in a hypoxic intrauterine environment. [24] Researches have shown that most early miscarriages are caused by an ischemic environment, increasing the concentration of serum IMA [25], and the oxidative stress is on the high side in an ectopic pregnancy, compared to normal pregnancy. [26]

Ischemia modified albumin has undergone a conformational change in the N-terminus and loses its ability to bind transitional metals (copper or cobalt), probably through a series of chemical reactions.

Ischemia-modified albumin is a relatively new biomarker in the identification of myocardial ischemia. IMA can be detected before troponin and has a high sensitivity of 82 % compared to traditional diagnostic tools. It is well known that IMA rises within minutes from the onset of cardiac ischemia and remains elevated for several hours after cessation of ischemia. [27] IMA also elevated in other conditions like pulmonary embolism, [28] thromboembolic occlusion of superior mesenteric artery, [29] acute stroke, [30] carbon monoxide poisoning. [31]

PATIENTS AND METHODS:

This a case-control study conducted in the department of Obstetrics and Gynecology at Azadi teaching hospital, Kirkuk, Iraq. from 1st of March 2018 to the end of December 2018. This study was approved by the scientific council of Obstetrics and Gynecology / Iraqi Board for Medical Specializations.

Eighty pregnant women were included in this study after signing on the informed consent and allocated to one of two groups:

1. Group 1: thirty-eight women diagnosed with an ectopic pregnancy at the first presentation.
2. Group 2: forty-two women with normal pregnancy confirmed by the abdominal US.

The diagnostic criteria for ectopic pregnancy were the beta HCG levels over 1500 IU/mL and the emptiness of the uterine cavity and cervical canal but a gestational sac seen in either adnexa or tube by transvaginal ultrasound scan.

Women with Systemic diseases, ruptured ectopic pregnancy, miscarriage, a history of smoking or substance abuse, the use of anti-inflammatory drugs and antioxidants were excluded from the study.

Blood samples were obtained during the admission period after confirmation of IUP or EP, just before surgical intervention or administration of medications related to EP. Centrifugation of specimens (15 minutes at 2000 rpm) took place within an hour of sample collection, and Serum IMA was measured using an enzyme-linked immune sorbent assay (ELISA) kit, according to the manufacturing company manual (Sunlong Biotech, China), which is based on biotin double antibody sandwich technology to assay IMA.

To eliminate the effect of albumin concentration on IMA, we adjusted the IMA results by using the following formula to calculate the A-IMA:

Adjusted IMA (A-IMA) = [(individual serum albumin concentration/median albumin concentration of the groups) X IMA] [23]

Patients with ectopic pregnancy (Group 1) were managed surgically, except 1 case was managed with a single dose of methotrexate (50 mg/m^2 intramuscularly). Further confirmation of EP was done by histopathological examination of surgical specimens.

All patients discharged home in good condition and with no complications.

Follow up for both groups was done (IUP until term with no complications and those with ectopic pregnancy group for one month following the intervention).

STATISTICAL EVALUATION:

Data were analyzed using the Statistical Package for Social Sciences (SPSS). The distribution of pregnant women and the comparison of general characteristics between both study groups was made. The mean of IMA and A-IMA was calculated, and found the correlation between A-IMA and maternal age, and BMI in each group was done. Receiver operating characteristic (ROC) curve analysis was used for prediction of A-IMA level as diagnostic of ectopic pregnancy and estimation of the sensitivity, specificity, and accuracy of the A-IMA marker depending on the cut off value constructed by ROC curve analysis.

RESULTS:

All women completed the study, and there was no statistically significant difference ($P \geq 0.05$) between study groups regarding age (P= 0.249), body mass index (BMI) level (P= 0.478), gestational age (P= 0.059), parity (P=0.054), and gravidity (P= 0.931).

The means of IMA and A-IMA in women with ectopic pregnancy were higher than that in women with normal pregnancy, and this difference in means was statistically significant (P= 0.001). Table 1 shows the comparison in means of IMA and A-IMA levels between the two groups.

Table 1: Comparison in means of IMA and A-IMA levels between ectopic and normal pregnancy.

Variable	Group A Ectopic Pregnancy Mean ± SD	Group B Normal Pregnancy Mean ± SD	P-Value
IMA Level (ng/ml)	1075.8 ± 43.28	884.6 ± 79.33	*0.001*
Adjusted IMA Level (ng/ml)	1074.6 ± 59.88	892.0 ± 153.58	0.001

Diagnostic accuracy for the test of ectopic pregnancy:

Receiver operating characteristic (ROC) curve analysis was used to predict the A-IMA level as a diagnostic of ectopic pregnancy. As shown in figure (1) and table (2), the cut point of A-IMA value was 980 ng/ml, so A-IMA > 980 ng/ml is predictive for diagnosis of ectopic pregnancy as a large significant area under the curve (AUC= 85%) indicating a significant association between higher level of A-IMA and diagnosis of ectopic pregnancy.

A-IMA was 97% sensitive, 69% specific, and 82.5% accurate as a marker for diagnosis of ectopic pregnancy.

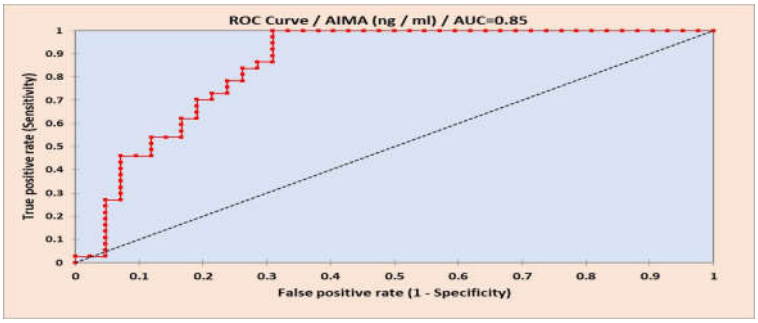

Figure 1: ROC curve analysis for prediction of A-IMA level as diagnostic of ectopic pregnancy.

Table 2: Diagnostic accuracy for the test of ectopic pregnancy.

A-IMA (ng/ml)	Cut-off value	Sensitivity	Specificity	PPV	NPV	Accuracy
	980	97%	69%	74%	97%	82.5%

Sensitivity, specificity, and accuracy of AIMA marker result:

Table 3 shows the sensitivity, specificity, and accuracy of the A-IMA marker result depending on the cut off value constructed by ROC curve analysis.

Table 3: Sensitivity, specificity, and accuracy of A-IMA marker result.

A-MIA Result	Ectopic Pregnancy		
	YES	NO	Total
Positive	37	13	50
Negative	1	29	30
Total	38	42	80

Comparison in the mean of A-IMA level between ectopic and normal pregnancy by maternal age and BMI:

It was clear that the mean of A-IMA level in group 1 was significantly higher than that in group 2 in both (20 – 34) and ≥ 35-year age groups (P=0.001). While the difference in mean of A-IMA in those aged < 20 was statistically not significant (P= 0.065).

Although there was no statistically significant difference (P= 0.089) in the mean of A-IMA level among study groups with normal BMI level, however; overweight and obese women have a statistically significant difference (P=0.001) in the mean of A-IMA levels, as the means in ectopic pregnancy was higher than that in normal pregnancy. This comparison is shown in table (4).

Table 4: Comparison of the mean of A-IMA level between ectopic and normal pregnancy by maternal age and BMI.

Variable	Total A-IMA Level		P-Value
	Study Groups		
	Ectopic Pregnancy Mean ± Std. Dev	Normal Pregnancy Mean ± Std. Dev	
Maternal Age (Years)			
< 20	1051.4 ± 60.16	888.1 ± 155.5	0.065
20 - 34	1076.4 ± 53.43	909.6 ± 160.9	0.001
≥ 35	1080.8 ± 71.21	827.8 ± 120.6	0.001
BMI Level (k/m2)			
Normal	1056.2 ± 45.31	979.38 ± 136.5	0.089
Overweight	1082.3 ± 59.86	855.4 ± 171.6	0.001
Obese	1081.8 ± 72.89	849.6 ± 114.4	0.001

The Correlation between A-IMA and maternal age in both groups was also calculated and shown in figure (2-A). There was no statistically significant correlation detected between A-IMA level and maternal age (r= 0.018, P= 0.877).

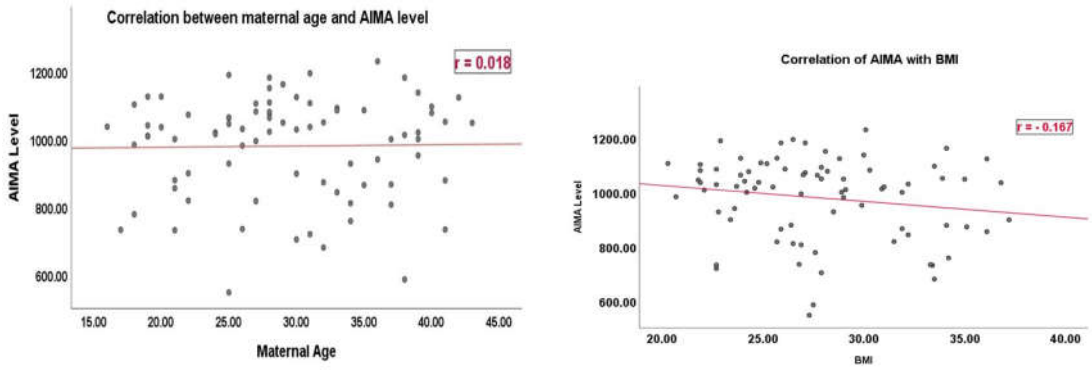

Figure 2: A showing the correlation between A-IMA and maternal age in both groups, B showing the correlation between A-IMA and BMI in both groups.

Furthermore, there was no significant correlation detected between A-IMA and BMI level (r= -0.193, P= 0.055), as shown in figure (2-B).

DISCUSSION:

Ectopic pregnancy is an unmitigated disaster of human production and is the most important cause of maternal morbidity and mortality in the first trimester with a significant cause of reduced childbearing potential. ([32])

The term 'oxidative stress' is defined as an imbalance between pro- and antioxidant capacity. Oxidative stress thinks to be implicated in many reproductive and pregnancy disorders, from subfertility, miscarriage, ectopic pregnancy to maternal vascular disease and preterm labor. ([33])

Antioxidant status is quite essential in protecting the fertilized ovum from oxidative stress. Ischemia modified albumin (IMA) is a form of albumin which loses its cobalt binding property when exposed to oxidative stress, which is a clinical chemistry assay that indirectly detects IMA by measuring the decreased binding capacity of albumin for cobalt. ([34])

IMA was first studied as an ischemia biomarker in cardiac diseases. (35) It was also increased in non-cardiac diseases and pregnancy-related problems such as eclampsia and pre-eclampsia and pregnancy itself. (36)

In our study, there was no statistically significant difference in maternal age, BMI, parity, and gravidity with p-value (0.249), (0.478), (0.054), and (0.931), respectively.

Although there is limited literature determined the role of IMA and A-IMA in the diagnosis of ectopic pregnancy, we found in our study that means of IMA and A-IMA in women with ectopic pregnancy were significantly higher than that in women with normal pregnancy (P= 0.001). This result agrees with the Bozkaya et al. study (23), who found that women with ectopic pregnancy had a significantly higher level of IMA and A-IMA than those observed in women in normal pregnancy.

By ROC curve analysis, the cut point of A-IMA value was 980 ng/ml, so AIMA > 980 ng/ml is predictive for diagnosis of ectopic pregnancy as a large significant area under the curve (AUC= 85%), indicating a significant association between higher level of A-IMA and diagnosis of ectopic pregnancy. A-IMA was 97% sensitive, 69% specific, and 82.5% accurate as a marker for diagnosis of ectopic pregnancy. Additionally, sensitivity = 97%, specificity = 69%, and accuracy of A-MIA marker was 82.5%, positive predictive value was 74%, while negative predictive value was 97%, depending on the cut off value constructed by ROC curve analysis.

In comparison to Bozkaya et al. study, the optimum cut-off point found in their study was 0.545 ABSU with a sensitivity of 81.6% and a specificity of 59%.([23])

We also found that there is no statistically significant correlation detected between A-IMA level with maternal age (r= 0.018, P= 0.877) and BMI level (r= - 0.193, P= 0.055), although the mean of A-IMA level was significantly higher in

both (20 – 34) and ≥ 35 age groups in the case group (P=0.001).

Regarding BMI level, no significant difference in the mean of A-IMA level among patients with normal BMI levels (P= 0.089). While significantly higher in overweight and obese women in the case group (P=0.001).

The explanation of the oxidative role in ectopic pregnancy can be determined by the fact that early stages of pregnancy are associated with oxidative stress presented between the maternal decidua and the villus placenta. This condition of hypoxia exists before the development of maternofetal circulation. Low oxygen tension at this stage stimulates blastocyst hatching, normal cell differentiation, and proliferation of cytotrophoblasts, which enables the establishment of the placenta before the period of rapid fetal growth occurring in the subsequent half of pregnancy. (37) Insufficient blood flow to the placenta may lead to a hypoxic environment and, after reoxygenation, lead to ischemia/reperfusion injury, with an increased free radical generation and subsequent oxidative tissue damage. (38) Besides, a decrease in blood flow to the uterus due to uterine contraction, changes in posture, and activity further exacerbate the state of oxidative stress. Hence throughout the pregnancy, a constant state of oxidative stress is maintained. So, oxidative stress depleted antioxidant status or the depletion of antioxidant status caused oxidative stress. Whichever the cause, the deleterious effects of oxidative stress may lead to an abnormal environment in the tube causing retention of an embryo within the Fallopian tube allowing early implantation and leading to ectopic pregnancy.

CONCLUSION:

There is an association between oxidative stress and ectopic pregnancy, and IMA is on the high side in ectopic tubal pregnancy. Further prospective clinical trials are needed with a larger number of patients to assess the role and correlation of IMA with different pregnancy complications, including the miscarriage, also to determine whether the difference in oxidative stress markers was a cause or a result of ectopic pregnancy, and to predict the level of the antioxidant depletion pre-pregnancy.

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