Serum angiopoietin-1 as a biomarker of missed miscarriage

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Abstract. Miscarriage is a prevalent issue that often occurs during pregnancy. Angiopoietin-1 screening may serve as the first diagnostic test which can be used to promptly establish the presence of a nonviable fetus, even as early as 6-8 weeks of gestation. The aim of the present study was to evaluate the effectiveness of serum angiopoietin-1 as a biomarker of missed miscarriage. The present cross-sectional cohort study conducted between June, 2021 and June, 2022. The study included a total of 100 women who were equally divided between the case group, including those with missed miscarriages, and the control group, which consisted of females with matched for age and gestational age who had a living fetus. Serum angiopoietin-1 levels were measured for all participants using the ELISA method. The results revealed that the mean angiopoietin-1 level was significantly lower in the case group compared to the control group (P<0.0001). At a cut-off point of ≤1,085 pg/ml, angiopoietin-1 was able to predict missed miscarriage with 88% sensitivity and 60% specificity. Regression analysis revealed that, of the laboratory tests, the single independent predictor of missed miscarriage was angiopoietin-1. Cases of missed miscarriage had a 5.5-fold [95% confidence interval, 2.89-10.47] greater risk of having an angiopoietin-1 level <1,085 pg/ml. On the whole, the present study demonstrates that angiopoietin-1 may be a promising marker for the prediction of missed miscarriage at a level ≤1,085 pg/ml with a good sensitivity and specificity.

Introduction

The most prevalent negative consequence of pregnancy is miscarriage. The documented incidence of pregnancy loss among women who have a missing menstrual period and test positive for pregnancy in urine ranges from 12 to 24%. The actual incidence of miscarriage is likely to be greater due to the occurrence of several preclinical losses prior to the absence of a menstrual cycle (1). In Iraq, the reported prevalence of abortion is 30% among pregnant women, while in the Kurdistan Region, it is 27.7% (2).

Currently, the threshold for viability is established at 24 weeks of gestation; however, it is anticipated that this threshold may be subject to modification in light of advancements in newborn care (3). Miscarriages may be categorized as either early (at <12 weeks of gestation) or late (at between 13 and 24 weeks of gestation) (4).

The glycoprotein known as angiopoietin-1 involves several physiological processes, including vascular development, angiogenesis and vascular permeability (5). Mice lacking angiopoietin-1 genes perish during prenatal development (6).

The identification of missed abortion may be accomplished by the use of a trans-vaginal ultrasound, with common practice being the repeated administration of an ultrasound in order to validate the diagnosis. Several studies have proposed the angiopoietin-1 level as the first diagnostic test with which to promptly establish the presence of a non-viable fetus, even as early as 6-8 weeks of gestation. Assessing the serum levels of angiopoietin-1 may help to reduce the psychological distress experienced by individuals who have had a missed abortion and need to undergo numerous ultrasounds (7-10). These encouraging results has provided an opportunity to explore its association with missed miscarriage, in order to more accurately determine the causes of missed miscarriage, and to examine potential therapies or preventive measures. The aim of the present study was to examine the effectiveness of the serum angiopoietin-1 level as a biomarker of missed miscarriage.

Patients and methods

Study participants and information. The present study was a case-control study conducted at the Department of Obstetrics and Gynecology at Baghdad Teaching Hospital, Baghdad, Iraq), during the period between June 1, 2021 and June 1, 2022. The present study was approved by the Council of the Iraqi Board of Medical Specialization (registered under EAC-2311). Prior to data collection, a statement of written informed consent to participate in the study as specified in the Declaration of Helsinki, was obtained from each patient. The confidentiality of all information was maintained by the use of a password-protected laptop, and the data were used only for research purposes.

The present study included 100 women who presented to the Gynecological Clinic at Baghdad Teaching Hospital diagnosed with a missed miscarriage determined using an

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ultrasound. The case group included 50 women with missed miscarriages, while the control group consisted of 50 women matched for age and gestational age with live fetuses. The inclusion criteria were as follows: Women with missed miscarriage in the first trimester (up to 13 weeks); the exclusion criteria were the following: Other types of miscarriage, women with medical diseases (particularly vascular and cardiac diseases).

Data were collected through the distribution of well-designed questionnaires including the following: General and clinical information, such as maternal age, educational level, occupation, residency, parity, and previous medical and surgical history. Moreover, collected data included the presentation of the cases (bleeding, vaginal, discharge, abdominal, pain, absence of pregnancy symptoms, or incidental finding). All participants were clinically evaluated by general, abdominal and per vaginal examination.

All women were referred for an ultrasound to corroborate the diagnosis of a miscarriage. A missed miscarriage was defined as a crown-rump length >7 mm in the absence of embryonic cardiac activity, or a mean gestational sac diameter >25 mm in the absence of a yolk sac or embryonic pole. The ultrasound was conducted by a radiologist with a Philips HD-11 ultrasound machine. In order to guarantee that the control cases did not experience miscarriage, they were subjected to follow-up phone calls until 24 weeks of gestation. The present study did not include cases that resulted in a delayed miscarriage.

Blood was withdrawn from patients and analyzed using Based on Mindray's continuous innovation in hematology field, BC-5000 and BC-5000 Reactive kit. This machine is based upon the fluorescence-activated cell sorting (FACS) technique. This machine was used to conduct the measurement of hemoglobin, white blood cells (WBCs; including subgroups) and platelets. The determination of the prothrombin time (PT), partial thromboplastin time, international normalized ratio (INR) and fibrinogen levels was performed using the Optical Coagulation Analyzer OCG-102 (Guangzhou Wondfo Biotech Co., Ltd.).

Determination of serum levels of angiopoietin-1. The levels of angiopoietin-1 were measured for all participants using the [Human Angiopoietin 1, ANG-I Kit, No.: YLA1052HU, Supplier: Gentaur, Catalog number: 576-201-12-1223].

A total of 5 ml venous blood was drawn from the participants and kept in a test tube and allowed to clot, then underwent centrifugation at 3,000 rpm (4,481.35 x g) for 15 min at 4˚C and plasma was separated and kept at -4˚C. At the time of measurement, the samples were thawed at room temperature, reagents were added then loaded onto an ELISA reader. The normal value provided by the manufacturer was 1,028.2-1,196.3 pg/ml.

Statistical analyses. Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 26 (IBM Corp.). Continuous data are expressed as the mean, standard deviation and range. Categorical data are presented using frequencies and percentages. The Shapiro-Wilk test was used to assess the normality of the variables. Parametric continuous variables were assessed using a two-tailed independent t-test. For non-parametric continuous variables, the Mann-Whitney U test was used. The association between categorical variables was evaluated using the Chi-squared test, and the Fisher-Freeman-Halton exact test was used when the predicted frequency was <5. The sensitivity and specificity of each cut-off point were estimated using receiver operator characteristic (ROC) curve analysis. The Youden J index test was used to determine the optimal cut-off point. Based on this cut-off point, the positive predictive value, negative predictive value and accuracy of the test were calculated. Binary logistic regression analysis was used to do univariate and multivariate analysis. Pearson's correlation analysis was performed to determine the correlation between the fibrinogen level with the angiopoietin-l level. A P-value <0.05 was considered to indicate a statistically significant difference.

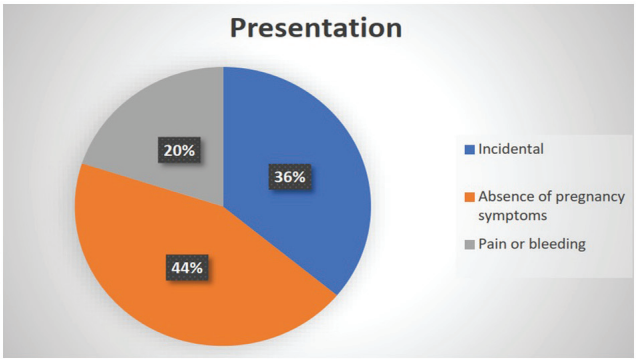

Figure 1. Clinical presentation of the case group (patients with missed miscarriage) in the present study.

Results

The mean maternal and gestational ages of the participants exhibited no significant difference between the case and control groups, eliminating these two confounders for the better estimation of the true effect of the remaining variables. The values for gravidity and parity also did not differ significantly between the two groups, however, the case group had a higher rate of previous miscarriage than the control (Table I).

The educational level of the participants differed significantly between the two groups; participants in the case group who had undergone secondary and higher education were associated with a higher rate of missed miscarriage compared with the control group. The case group exhibited a higher prevalence of irregular antenatal care visits in the context of previous miscarriages than the control group (Table II). The presentation of participants in the case group was mainly due to the absence of pregnancy symptoms, as shown in Fig. 1.

Analyses revealed that the white blood cell (WBC) count was higher in the cases of miscarriage than in the controls, while fibrinogen levels were lower in the cases of miscarriage than the controls (Table III). The mean angiopoietin-1 level was significantly lower in the case group than the control group (Table IV).

There was a significant positive correlation between the fibrinogen level and angiopoietin-1 level (Table V); the levels of both markers tended to decrease in cases of miscarriage (Tables III and IV).

Table I. Demographical data distribution of the patients in the present study.

	Case group		Control group		
Variables	Mean	SD	Mean	SD	P-value
Maternal age (years)	29.9	6.3	27.6	7.2	0.105
Gestational age (weeks)	8.8	1.5	9.2	3.0	0.454
Gravida	4.1	2.3	3.8	1.8	0.502
Para	1.9	1.7	2.5	2.0	0.117
Miscarriage	1.0	1.3	0.5	0.8	**0.020**

Values in bold font indicate statistically significant differences (P<0.05).

Table II. Educational level and regularity of antenatal care visits.

Variables	Case group (n=50)	Control group (n=50)	Total	P-value
Educational level, n (%)				
Illiterate	6 (12)	5 (10)	11 (11)	**<0.0001**
Primary	14 (28)	35 (70)	49 (49)	
Secondary	20 (40)	9 (18)	29 (29)	
Higher	10 (20)	1 (2)	11 (11)	
Antenatal care visits in previous miscarriage, n (%)				
Regular	32 (64)	43 (86)	75 (75)	**0.011**
Irregular	18 (36)	7 (14)	25 (25)	

Values in bold font indicate statistically significant differences (P<0.05).

Table III. Distribution of investigations between the two groups.

	Case group (n=50)		Control group (n=50)		
Variables	Mean	SD	Mean	SD	P-value
WBC	10.56	1.61	9.91	1.54	**0.042**
HB	10.57	1.09	10.38	1.03	0.357
PT	13.68	2.7	14.2	2.89	0.355
PTT	36.08	4.44	34.58	4.8	0.108
INR	0.85	0.23	0.9	0.22	0.290
Fibrinogen	215.16	48.03	240.3	41.96	**0.006**

Values in bold font indicate statistically significant differences (P<0.05). WBC, white blood cell; HB, hemoglobin; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio.

The estimation of the true association was further investigated using multivariate analysis which revealed that both the educational level and angiopoietin-1 level were independent predictors of missed miscarriage, as shown in Table VI.

The calculation of the predictive ability of angiopoietin-1 was performed using ROC curve analysis. It was found that angiopoietin-1 could efficiently predict missed miscarriage with an area under the curve of 0.936, and with ab analysis accuracy equal to 86% (Fig. 2). The predictive ability of angiopoietin-1, calculated at a level below or equal to the cut-off point of ≤1,085 pg/ml (the point with the optimal sensitivity and specificity illustrated on the curve), at which there was 5.5-fold greater risk of having a missed miscarriage (odds ratio, 5.5). With this cut-off point, angiopoietin-1 was able to predict missed miscarriage with 88%

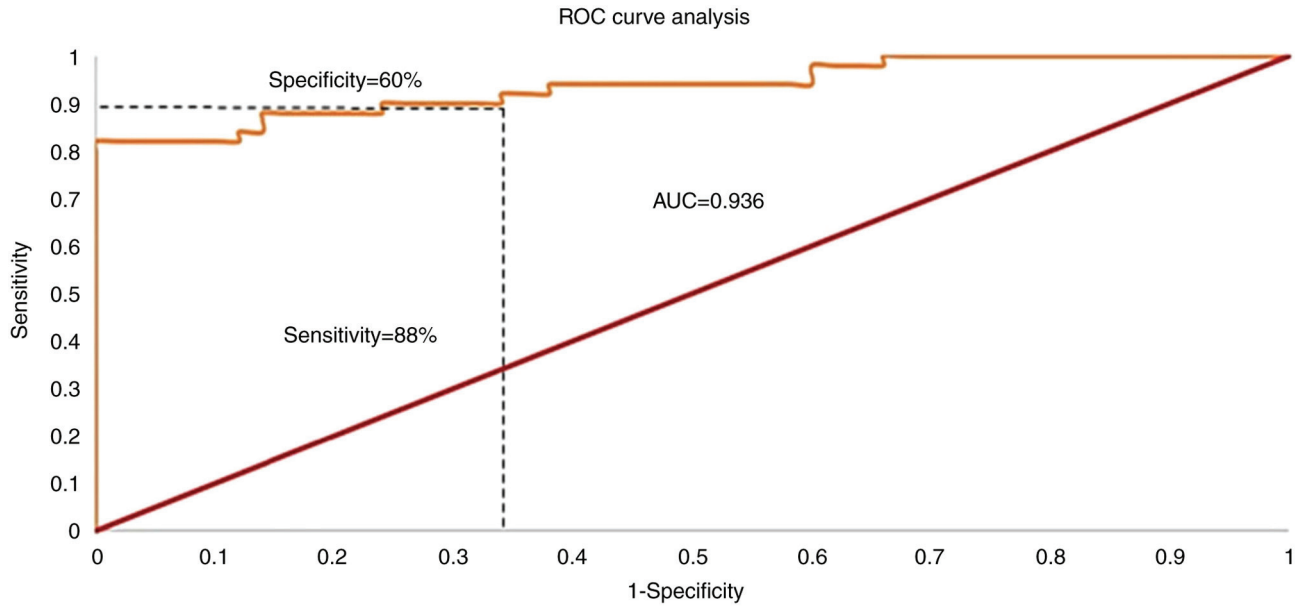

Figure 2. ROC curve analysis. ROC, rreceiver operating characteristic.

Table IV. Angiopoietin-1 levels in both groups.

Group	Mean	SD	Min	Max	P-value
Case	840	174	543	1,165	**<0.0001**
Control	1,157	89	1,037	1,432	

Angiopoietin-1 levels were measured in pg/ml. Values in bold font indicate statistically significant differences (P<0.05).

Table V. Analysis of the correlation between the angiopoietin-1 and various parameters.

	Angiopoietin-1 level	
Variables	Pearson's correlation (R value)	P-value
WBC	-0.162	0.108
HB	-0.107	0.290
PT	0.084	0.407
PTT	-0.096	0.343
INR	0.151	0.134
Fibrinogen	0.219	**0.028**

Correlation analysis revealed a significant positive correlation between the fibrinogen level with angiopoietin-1, i.e.; both tended to decrease in cases of miscarriage. Values in bold font indicate statistically significant differences (P<0.05). WBC, white blood cell; HB, hemoglobulin; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio.

sensitivity and 60% specificity, and with an accuracy of 86% in prediction of missed miscarriage (Table VII).

Table VI. Univariate and multivariate analysis of predictors of miscarriage.

Variables	Univariate analysis P-value	Multivariate analysis P-value
Maternal age	0.105	0.099
Gestational age	0.454	0.257
Gravida	0.502	0.84
Para	0.117	0.686
Miscarriage	**0.020**	0.782
Educational level	**<0.0001**	**0.006**
Antenatal care visit	**0.02**	0.064
WBC	**0.042**	0.583
HB	0.357	0.837
PT	0.355	0.067
PTT	0.108	0.525
INR	0.29	0.176
Fibrinogen	**0.006**	0.105
Angiopoietin-1 level	**<0.0001**	**0.007**

Values in bold font indicate statistically significant differences (P<0.05). WBC, white blood cells; HB, hemoglobulin; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio.

Discussion

The global incidence of missed miscarriage is increasing; however, the exact etiology for this remains unknown. A number of predictive modules and numerous markers are under investigation to estimate their association with miscarriage (11); however, inflammatory markers have recently gained specific attention, as miscarriage could be both the cause and effect of the inflammatory process. In the present study, the maternal

Table VII. Predictive ability of angiopoietin-1 for missed miscarriage.

Predictor	Value
Area under the curve	0.936
95% Confidence interval	0.887-0.984
Cut-off point	1085
Sensitivity	88%
Specificity	84%
Positive predictive value	84.6%
Negative predictive value	87.5%
Accuracy	86%
Odds ratio	5.5
95% Confidence interval	2.89-10.47

and gestational ages, which are the main confounders, did not differ significantly between the two groups. The association between maternal age and miscarriage has been well-established (12-14). To avoid the biased result that could result from this confounder, the present study included age-matched patients in the study groups. The gravidity and parity did not differ significantly between the two groups; similar results were obtained in the study by Coomarasamy *et al* (15).

The rate of previous miscarriage was significantly higher in the case group when compared with the control group; a similar result was observed in the study by Quenby *et al* (1). This could be attributed to hidden chronic inflammatory possess that caused such a significantly increased rate of miscarriage, as suggested in the study by Kozyreva *et al* (16).

In the present study, the educational level was significantly different between the two groups. The control group had a higher rate (70%) of cases at the primary education level compared with 28% of this category in the miscarriage group. This contradicts the findings presented in the study by Baqui *et al* (17), which found that cases with a low educational level tended to have a higher rate of pregnancy loss. Herein, the rate of irregular antenatal care visits in previous missed miscarriages was more prevalent in cases of missed miscarriage than in the controls; this finding was in agreement with that in the study by Madu (18).

The mean WBC in the present study, and in a previous study (19) was higher in cases of missed miscarriage than in the controls. This reflects multiple factors that may be associated with the pathogenesis of missed miscarriage. The mean hemoglobin level did not markedly differ between the two groups, a finding which is in accordance with the findings of other studies (11,19).

In the present study, the coagulation profile did not markedly differ between the two groups. Nasr *et al* (20) found that the PT and international normalized ratio were significantly prolonged in cases of miscarriage compared with the controls. This may be attributed to their inclusion of recurrent miscarriage cases that may associated with different pathophysiological processes from missed miscarriage. In the study by Jiang *et al* (21), coagulation profiles in the form of PT, partial thromboplastin time and INR did not differ in cases of missed miscarriage when compared with the controls, unless the patient had already disseminated intravascular coagulation, which per se was associated with coagulation abnormalities.

In the present study, in comparison to the control group, it was found that the mean fibrinogen and angiopoietin-1 levels were substantially lower in cases of missed miscarriage; a significant positive correlation was also found between these markers. Comparable outcomes have been reported by several studies (22-26). It is important to note that angiopoietin-1 is responsible for the growth and maturation of vascular tissue, which is a necessary component of placental development and the progression of pregnancy. Rao *et al* (26) proposed that the absence of new blood vessel formation is indicative of pregnancy failure.

In the present study, regression analysis revealed that, of the laboratory tests, the single independent predictor of missed miscarriage was angiopoietin-1. The angiopoietin-1 level in normal pregnancy during the first trimester (the control group) ranged from 1,037-1,432 pg/ml. Rao *et al* (26) found a range of 1,028.5-1,196.3 pg/ml, whereas Abozeid *et al* (7) found a range of 793.9-1,277.6 pg/ml; this difference between the studies may be related to the type of kit used. In the present study, following the application of ROC curve analysis, ot was found that an angiopoietin-1 level ≤1,085 pg/ml was associated with a sensitivity of 88%, specificity of 84%, positive predictive value of 84.6%, and negative predictive value of 87.5%. Cases of missed miscarriage had a 5.5-fold greater risk (odds ratio, 5.5; 95% confidence interval, 2.89-10.47) of having an angiopoietin-1 level <1,085 pg/ml. Comparable results were found in the study by Abozeid *et al* (7) with a sensitivity and specificity of 87.5 and 90%, respectively. These minor variations are likely due to the use of different ELISA kits with varying detection ranges.

Of note, a limitation of the present study which should be mentioned was the small sample size. Thus, further studies with larger sample sizes are required in the future to further confirm the findings.

In conclusion, The present study demonstrates that the serum level of angiopoietin-1 is significantly reduced in cases of missed miscarriage, as early as 6-8 weeks of gestation, when compared to that of a viable intrauterine pregnancy of similar gestational age. Angiopoietin-1 may thus be employed as a marker for the prediction of missed miscarriage with great specificity and sensitivity.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

ZF was involved in the conception and design of the study, in the literature search, clinical analysis, data analysis, statistical analysis, in the preparation of the manuscript, and in the reviewing of the manuscript. WI was involved in the conception and design of the study, as well as in data analysis, in the preparation of the manuscript and in the reviewing of the manuscript. Both authors have read and approved the final manuscript. ZF and WI confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved by the Council of the Iraqi Board of Medical Specialization (registered under EAC-2311). Prior to data collection, a statement of written informed consent to participate in the study as specified in the Declaration of Helsinki, was obtained from each patient. The confidentiality of all information was maintained by the use of a password-protected laptop, and the data were used only for research purposes.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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