

Original Article

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

SJIF Impact Factor: 6.711

ISSN: 2457-0400 Volume: 9. Issue: 5 Page N. 221-224 Year: 2025

www.wjahr.com

THE ROLE OF ANGIOPOIETIN-1 IN MISSED ABORTION: A CASE CONTROL STUDY CONDUCTED IN MOSUL CITY-IRAQ

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Article Received date: 09 March 2025 Article Revis

Article Revised date: 30 March 2025

Article Accepted date: 19 April 2025



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ABSTRACT

Background: The incidence of missed abortion cannot be accurately estimated because the incidence of conception is unknown. Angiopoietin-1 is a member of the growth factor family and is an angiogenic protein. The placental syncytiotrophoblasts and mesenchymal cells both release it, as a result its alternating levels can paly a role in detecting abortion. Objectives: Is to determine whether serum angiopoietin-1 is a useful indicator of missed abortions in the first trimester among pregnant ladies in Mosul City. Methods: The study is a descriptive, case control study, conducted in the department of Gynaecology and Obstetrics of Al Khansa'a Teaching Hospital in collaboration of the laboratories department of the hospital between the 11th of April 2024 to the end of January 2025. The questionnaire was divided into two main sections. The first section provides demographic information about the study participants. The second section covers laboratory findings of the study participants. Results: The study included 100 first trimester pregnant women, whose pregnancy also confirmed by ultrasound. Of them; 50 women with confirmed ultrasound of missed abortion (the cases) and 50 women with confirmed ultrasound of viable fetuses (the controls). Furthermore; the mean age of the study participants are 24.53 ± 5.26 years, while; the mean of gestational ages of the study participants are 8.97 ± 1.37 weeks. Additionally; statistically significant difference between the study groups found regarding gravity (more gravity found among cases group), parity (more parity among cases group), abortion (more abortion among cases group). It's evident that angiopoietin-1 is statistically significant different between cases and controls with higher mean levels among controls group. From the other hand; no statistically significant difference is found regarding mean of fibrinogen, APTT, PT and INR. Lastly; the cut off point of ≤ 1.002 can detects viable fetus from missed abortion (total area of 0.037, P-value of 0.001), with sensitivity of 92 %, specificity of 90 %, positive predictive value of 90.1 %, negative predictive value of 91.8% and total accuracy of the test of 91 %. Conclusion: According to the current study, pregnant women who have missed an abortion have considerably lower serum levels of angiopoitin-1 than those in a normal viable and matched gestation pregnancy with high sensitivity and specificity. It might suggest that it plays a part in the pathophysiology of missed abortions.

KEYWORDS: Pregnancy loss, First trimester, Mosul, Iraq.

1- INTRODUCTION

Abortion is defined by the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and the National Center for Health Statistics as any pregnancy termination, whether induced or spontaneous, that occurs before 20 weeks of gestation or with a fetus born weighing less than 500 grams.^[1-3] The length of pregnancy and the weight of the fetus are typically used to define abortion for statistical and legal purposes.^[3-4] The incidence of missed abortion cannot be accurately estimated because the incidence of conception is unknown.^[5] Fifteen-twenty percent of pregnancies that

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are clinically identified end spontaneously, and more will be passed so early without detection.^[6-7]

As mothers age, the rate of miscarriages rises. Miscarriages are more common in women under the age of 20 and over the age of 35, and their likelihood increases with increasing parity and the number of prior losses.^[8] Although miscarriages rarely result in maternal death, they can cause morbidities such as psychological stress, bleeding, infection, secondary infertility, and repeated miscarriages in future pregnancy.^[9] Silent miscarriage occurs when the uterus does not attempt to

expel the fetus even after the fetal death. During this period, the body continues to release hormones despite the fetal death.^[10-11] These patients may have lost some of the early pregnancy symptoms and lack uterine development.^[12] Other than prolonged amenorrhea, many women experience no symptoms during this time. Weekly fibrinogen levels should be monitored until the fetus and placenta have been expelled since coagulation problems could appear. Consumptive coagulability and hypofibrinogenemia may result from keeping the fetus in the uterus for more than five weeks after the death.^[13] Missed abortions typically end spontaneously, and the process of ejection is similar to any other spontaneous abortion.^[14]

Angiopoietin-1 is a member of the growth factor family and is an angiogenic protein.^[15] The placental syncytiotrophoblasts and mesenchymal cells both release it.^[16] Thus, the study aims to determine whether serum angiopoietin-1 is a useful indicator of missed abortions in the first trimester among pregnant ladies in Mosul City.

PATIENT AND METHODS

The study is a descriptive, case control study, conducted in the department of Gynaecology and Obstetrics of Al Khansa'a Teaching Hospital in collaboration of the laboratories department of the hospital between the 11th of April 2024 to the end of January 2025. Ethical approval was obtained from the ethical committee at Nineveh Directorate of Health before starting of the study. The study included 100 first trimester pregnant women, whose pregnancy also confirmed by ultrasound. Of them; 50 women with confirmed ultrasound of missed abortion (the cases) and 50 women with confirmed ultrasound of viable fetuses (the controls). The samples of both groups were selected randomly from the study settings.

Patients were asked about their presenting problem, age, last menstrual period, obstetrical history, gynecological history, medical and surgical history. Furthermore; General, vital signs, and systemic examinations were done for all of them. Moreover; maternal blood samples were taken from both groups before intervention. The samples were then sent to the labs for coagulation profile, full blood count, random blood sugar, and blood group/cross match, if necessary. The ELISA test was used to assess the serum angiopoietin-1 level in both groups by drawing three milliliters of blood from a visible vein, centrifuged for ten minutes at 10,000 rpm, and then the separated serum was stored at -20°C. This method relies on biotin double antibody sandwich technology. Abdominal ultrasonography was used to evaluate fetus viability and gestational age.

Patient whose conceived after in vitro fertilization or ladies with multiple pregnancies or those a history of chronic medical disorders (e.g., thyroid, liver, renal, diabetic, hypertension), blood dyscrasias (e.g., hypercoagulopathy or bleeding tendencies), and having history of malignancy are excluded from the study.

Statistically analysis done by using the SPSS (scientific package for social sciences) version 30.0 software. Descriptive statistics, such as frequencies and percentages, were used to present categorical variables in tables and figures. The chi-squared (χ 2) test was used to determine the significance of differences between cases and controls groups. The T-test is used to compare mean and median values for continuous variables. Pearson correlation demonstrates the correlation between continuous data. The ROC curve demonstrates more sensitive and specific cutoff points. P-values less than 0.05 were regarded as statistically significant.

3-RESULTS

The study includes 100 pregnant ladies, the mean age of the study participants are 24.53 ± 5.26 years, while; the mean of gestational ages of the study participants are 8.97 ± 1.37 weeks, with no statistically significant difference found between the study groups regarding these variables. Moreover; statistically significant difference between the study groups found regarding gravity (more gravity found among cases group), parity (more parity among cases group), abortion (more abortion among cases group). As shown in table 3.1.

 Table 3.1: Basic information of the study participants.

Variable	Cases = 50	Controls = 50	P-value	
Maternal age, year	24.38 ± 5.21	24.78 ± 5.32	0.829	
Gestational age, weeks	8.82 ± 1.54	9.13 ± 1.21	0.438	
Gravidity:				
-Less than five	33 (66%)	42 (84%)	0.011	
-More than five	18 (36%)	8 (16%)	0.011	
Parity:				
0	17 (34%)	26 (52%)		
1-3	15 (30%)	19 (38%)	0.042	
More than 3	18 (36%)	15 (30%)		
Abortion:				
-Yes	20 (40%)	8 (16%)	0.017	
-No	30 (60%)	42 (84%)	0.017	

Table 3.2 shows laboratory investigations of the study participants. It's evident that angiopoietin-1 is statistically significant different between cases and controls with higher mean levels among controls group.

From the other hand; no statistically significant difference is found regarding mean of fibrinogen, APTT, PT and INR.

Variable	Cases = 50	Controls = 50	P-value
Fibrinogen level, mean ± Standard deviation	207.89 ± 52.82	213.35 ± 58.36	0.340
APTT, mean ± Standard deviation	29.28 ± 3.21	27.99 ± 3.87	0.121
PT, mean ± Standard deviation	16.29 ± 1.37	15.71 ± 1.29	0.239
INR, mean ± Standard deviation	1.23 ± 0.13	1.18 ± 0.19	0.892
Angiopoietin-1 Pg./ml, mean± Standard deviation	782.30 ± 154.59	1461 ± 381.31	<0.001

Tables 3.3 and 3.4 illustrate the cut off point of ≤ 1.002 can detects viable fetus from missed abortion (total area of 0.037, P-value of 0.001), with sensitivity of 92 %,

specificity of 90 %, positive predictive value of 90.1 %, negative predictive value of 91.8% and total accuracy of the test of 91 %.

 Table 3.3: Area under the curve of Angiopoitin-1.

Variable	A 1000	Standard error	P-value	Confidence interval	
variable	Area			Upper limit	Lower limit
0.932	0.037	0.016	0.001	0.905	0.965

Table 3.4: Accuracy measurements of the Angiopoitin-1.

Variable	Ultrasound findings		Total numbers	
variable	Demised fetus Viable fetus			
Positive	46	5	51	
Negative	4	45	49	
Total number	50	50	100	
Sensitivity = 92 %	Specificity = 90 %	Positive predictive value =	Negative predictive value =	
		90.1 %	91.8 %	
Accuracy of the test = 91%				

4- DISCUSSION

Missed abortion occurs when the dead products of conception remain in the uterus for days or weeks with a closed cervical os. Diagnosis is crucial prior to intervention and avoids interruption of a potentially live intrauterine pregnancy.^[17]

In the present study, significant differences were found between cases with missed abortion and those with normal preceding pregnancy regarding gravidity, parity and abortion. Genetics may be a contributing factor for these facts, comparable results were agreed by Wei-Zhen Jiang et al.^[18]

Regarding laboratory investigations; this study showed no significant difference between cases and controls regarding the mean of fibrinogen, APTT, PT and INR. Which is consistent with Lingna Huang.^[19]

From the other hand; the mean of angiopoietin-1 levels was founded to be significantly higher among control group as it is an angiogenic factor, and associated with normal pregnancy advancement. A decrease in its level indicates a missed abortion. Comparable results obtained from Maryam Rao et al.^[20]

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Moreover; this study found that the optimum cut off point for angiopoietin-1 level is 0.932 Pg./ml which can detects viable fetus from missed abortion which is closed to what is found by Maha Mohammed Jasim Al Bayati et al (0.951 Pg./ml).^[21]

The study's findings are limited by a small sample size of women from only one hospital, which may not be representative of all of Mosul hospitals. However; larger sample from different districts may provide a more comprehensive view of the role of angiopoietin-1 in detection of missed abortion.

5- CONCLUSION AND RECOMMENDATION

According to the current study, pregnant women who have missed an abortion have considerably lower serum levels of angiopoitin-1 than those in a normal viable and matched gestation pregnancy with high sensitivity and specificity. It might suggest that it plays a part in the pathophysiology of missed abortions.

ACKNOWLEDGEMENT

We are grateful for the help provided by the medical team at Al Khansa'a Teaching Hospital, as well as the careful consideration received from the Nineveh Directorate of Health. Without the help of each of these individuals, this study would not have been possible.

Conflict of intertest

About this study, the authors disclose no conflicts of interest.

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