

Possible Association of Serum Angiopoietin-1 Levels with Missed Miscarriages During the First Trimester of Pregnancy: A Prospective Case-Control Study on Iraqi Women

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Abstract—Background: Missed miscarriage represents a significant proportion of first-trimester pregnancy losses and is often asymptomatic, making early diagnosis challenging. Impaired placental angiogenesis plays a central role in its pathophysiology. Angiopoietin-1 is a key regulator of vascular stability and placental microvascular development, and its reduction may reflect early placental dysfunction. **Aim of the Study:** To evaluate the role of angiopoietin 1 as a biomarker for first trimester missed miscarriage. **Patients and Methods:** prospective case-control study conducted at Babil Teaching Hospital for Maternity and Children over a ten-month period from November 2024 to August 2025. A total of 100 pregnant women in the first trimester were included and divided into two equal groups: 50 women with ultrasound-confirmed missed miscarriage (cases) and 50 women with viable pregnancies (controls). Demographic, clinical, and obstetric data were collected. Serum Ang-1 levels were measured using enzyme-linked immunosorbent assay. **Results:** The mean maternal age did not differ significantly between the missed miscarriage group (30.2 ± 5.4 years) and the control group (28.9 ± 6.1 years). The mean gestational age was (9.2 ± 1.8) in the missed miscarriage group and (8.1 ± 1.3) in the control group, parity and history of previous miscarriage also comparable between the two groups ($p > 0.05$). Mean serum Angiopoietin-1 levels were significantly lower in women with missed miscarriage compared with controls (635.7 ± 119.9 pg/mL vs. 977.1 ± 220.6 pg/mL; $p < 0.001$). ROC curve analysis showed that a cut-off value of ≤ 780 pg/mL predicted missed miscarriage with a sensitivity of 63.6%, specificity of 97.9%, positive predictive value of 87.5%, negative predictive value of 90%, and an area under the curve of 0.936, indicating excellent diagnostic performance. **Conclusions:** Maternal serum Angiopoietin-1 levels are significantly reduced in first-trimester missed miscarriage. Serum Angiopoietin-1 showed good diagnostic accuracy and may serve as a useful biochemical marker.

Keywords— Angiopoietin-1, First Trimester of Pregnancy, biomarker, pathophysiology, missed miscarriage.

I. INTRODUCTION

Spontaneous miscarriage is defined as the spontaneous loss of a pregnancy prior to viability, taken legally in the UK as 23 weeks and 6 days of gestation. Beyond this gestation, fetal demise is classified as a stillbirth. The majority of first-trimester miscarriages occur below 12 weeks' gestation with an overall rate of around 20%. (Alves et al., 2023).

Angiopoietin-1 (Ang-1) is a key protein involved in the development and stabilization of blood vessels during pregnancy, particularly in the formation of the placental vasculature. It works by binding to the Tie2 receptor on endothelial cells, promoting vessel maturation and stability. In normal pregnancy, Ang-1 helps maintain a proper balance with Angiopoietin-2 (Ang-2), which promotes vascular remodeling. This balance is essential for adequate trophoblast invasion, placental development, and proper maternal-fetal circulation. (Kappou D et al., 2015).

In cases of missed miscarriage, Ang-1 levels are often significantly decreased. This reduction may lead to impaired vascular development and instability of the placental circulation. As a result, the embryo may not receive sufficient oxygen and nutrients, contributing to its demise. Since the embryo or fetus is no longer viable but remains in the uterus, this vascular insufficiency is thought to play a central role in

the pathophysiology of missed miscarriage (Wälchli et al., 2023).

The altered expression of Ang-1 in missed miscarriage also suggests that it may have potential as a biomarker for early pregnancy failure. Measuring Ang-1 levels could help in identifying pregnancies at risk of miscarriage, especially in cases where clinical symptoms are absent. Therefore, Ang-1 is not only important in maintaining healthy pregnancy progression but may also serve as a diagnostic or prognostic indicator in the context of missed miscarriage (Dugas et al., 2022). Therefore, the aim of this research to assess the level of angiopoietin 1 and its possible role as diagnostic a biomarker in women with first trimester missed miscarriage.

Early pregnancy loss can be classified into different types, each with distinct clinical and diagnostic features:

Threatened Miscarriage: Vaginal bleeding occurs, but the cervix remains closed, and fetal cardiac activity is present. The pregnancy may still continue normally (Hendriks et al., 2019).

Inevitable Miscarriage: Vaginal bleeding is accompanied by cervical dilation, indicating that pregnancy loss is unavoidable. (Nepiyivoda and Rvvak, 2020).

Incomplete Miscarriage: Some, but not all, products of conception have passed, leading to continued bleeding and cramping. (Redinger and Nguyen, 2024).

Complete Miscarriage: The entire gestational sac and fetus are expelled from the uterus, resulting in resolution of symptoms. (Shaker and Smith, 2022). (pan and vaginal bleeding).

Missed Miscarriage: The embryo or fetus has died, but there are no immediate signs of miscarriage, and the products of conception remain in the uterus (Devall and Coomarasamy, 2020).

Septic Miscarriage: A miscarriage complicated by intrauterine infection, often presenting with fever, foul-smelling discharge, and uterine tenderness. (Mariappa *et al.*, 2017).

Missed miscarriage accounts for approximately 10-15% of clinically recognized pregnancies, with the true incidence likely higher due to early pregnancy losses that go undiagnosed (Ralph *et al.*, 2020). Additional epidemiological data indicate that lifestyle and environmental factors contribute significantly to the risk of missed miscarriage. Poor nutritional status, exposure to environmental toxins, occupational hazards, and maternal infections are all contributing risk factors (Quenby *et al.*, 2021).

Based on these considerations, this study primarily aims to evaluate the potential association between maternal serum Ang-1 levels and missed miscarriage during the first trimester of pregnancy. Specifically, the research investigates the clinical utility of Ang-1 as an early diagnostic or prognostic biomarker to complement traditional screening tools in identifying non-viable pregnancies before clinical symptoms manifest.

II. METHODOLOGY

2.1. Study Design

Prospective case-control study designed to evaluate the possible association between serum (Ang-1) levels and missed miscarriage in the first trimester of pregnancy.

2.2. Study Setting

The study was conducted at Babil Teaching Hospital for Maternity and Children From emergency department and outpatient clinic, Babil province, Hilla, Iraq, over a period of ten months, from November 2024 to August 2025.

Data collection was conducted prospectively after obtaining approval from the Iraqi Board of Medical Specializations / Scientific Council of Gynecology and Obstetrics.

2.3. Ethical approval

1. The study protocol was approved by the Iraqi Board of Medical Specializations / Scientific Council of Gynecology and Obstetrics (the number of the approval is 675A on 5-12-2024)

2. Verbal consent was obtained from all the patients during data collection and blood sampling.

2.4. Study Population

The study included a total of 100 pregnant women divided into two groups:

- Group A (Cases): 50 women diagnosed with missed miscarriage in the first trimester (6-13 weeks gestation)

confirmed by ultrasound showing absence of fetal cardiac activity.

- Group B (Control): 50 women with viable first-trimester pregnancies, matched with Group A in terms of gestational age.

2.5. Inclusion Criteria

1. Confirmed Singleton intrauterine pregnancy with gestational age less than 14 weeks (based on last menstrual period and/or ultrasound).

2. For Group A (Cases): women with diagnosed missed miscarriage in the first trimester

3. For Group B (Control): women with confirmed viable pregnancy in the first trimester

2.6. Exclusion Criteria

To ensure a highly controlled study cohort and isolate the specific variables under investigation, specific exclusion criteria are strictly applied to eliminate confounding maternal factors. Potential participants are excluded if they have a history of recurrent miscarriage, defined as two or more previous pregnancy losses, which helps rule out established parental genetic, structural, or recurring autoimmune factors. Additionally, the presence of chronic systemic maternal diseases—such as pre-existing diabetes, hypertension, thyroid disorders, or autoimmune conditions—serves as grounds for exclusion, as these pathologies can independently compromise pregnancy viability or alter baseline biochemical markers. Finally, patients presenting with a septic miscarriage or any acute infection during the current pregnancy are omitted from the study to prevent the severe inflammatory and infectious processes from skewing the hematological and biomarker data.

2.7. Sample Collection

Approximately 5 ml of venous blood was collected from each participant using aseptic technique. Blood samples were drawn by laboratory personnel into plain tubes, allowed to clot at room temperature, and then centrifuged at 3000 rpm for 10 minutes to separate the serum. The obtained serum samples were stored at -20°C in the hospital laboratory until analysis.

Serum (Ang-1) levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit: Elabscience® Human ANG1 (Angiopoietin 1) ELISA Kit (Catalog No. E-EL-H0246), following the manufacturer's instructions.

2.8. Data Collection

A paper questionnaire was prepared for each participant to collect the required data. The collected information included the following:

2.8.1. History:

When evaluating a patient in an obstetric setting, a comprehensive history must be established immediately to guide clinical management and risk stratification. The assessment begins with the patient's baseline demographics and current pregnancy data, specifically capturing maternal age and the exact gestational age at presentation, both of which heavily influence the differential diagnosis for any

presenting symptoms. This is followed by a detailed obstetric history, documenting parity and any previous miscarriages or pregnancy losses to identify recurrent patterns or structural risks. Furthermore, the clinician must explore the patient's past medical history with specific focus on chronic conditions such as diabetes, hypertension, and thyroid disease alongside any past surgical history, particularly prior uterine surgeries which impact delivery planning. Finally, the history is completed by investigating social factors, including smoking and alcohol consumption, and a thorough drug history to screen for potential teratogenic exposures.

2.8.2. Examination:

The physical assessment of the obstetric patient requires a systematic approach, moving logically from a baseline systemic evaluation to focused regional examinations. The evaluation begins with a general examination to assess the patient's level of consciousness and establish baseline vital signs, including blood pressure, pulse rate, temperature, and respiratory rate, which serve as the primary indicators of maternal hemodynamic stability or systemic infection. Following the general assessment, an abdominal examination is performed to evaluate uterine size, estimate gestational age, assess fetal lie and presentation, and check for any localized tenderness or contractions. Finally, a vaginal examination is conducted when clinically indicated to assess for cervical changes, evaluate the nature and extent of any vaginal bleeding or fluid loss, and determine the progress of labor, ensuring strict aseptic technique or avoiding digital examination altogether if placenta previa or ruptured membranes are suspected.

2.8.3. Laboratory investigations:

The baseline laboratory workup incorporates standard hematological screens alongside specific vascular and coagulation biomarkers to comprehensively evaluate maternal health and clotting function. Initial assessment requires a Complete Blood Count (CBC) to check hemoglobin levels for anemia and monitor platelet and white blood cell counts, paired with ABO and Rh blood grouping to identify potential maternal-fetal blood type incompatibilities that necessitate Rho(D) immune globulin prophylaxis. Vascular integrity and angiogenic balance are evaluated through plasma Ang-1 levels, which serve as a critical biomarker for endothelial stability and placental development. Finally, the maternal coagulation profile is fully quantified through plasma fibrinogen levels alongside Prothrombin Time (PT), Partial Thromboplastin Time (PTT), and the International Normalized Ratio (INR) to establish a baseline for hemostatic function and rule out consumptive coagulopathies.

2.8.4. Imaging:

All patients underwent ultrasound examination to confirm cases of missed miscarriage and viability in control group. The imaging was performed on the same day as blood sample collection, using the Philips HD 11XE (Japan) machine available at the hospital. Either abdominal ultrasound performed using a standard abdominal probe with frequency 1–7 MHz or transvaginal ultrasound using vaginal probe with frequency 2–11 MHz.

2.9. Statistical Analysis

Data analysis was done using Statistical Package for Social Sciences (SPSS) version 27 for Microsoft® Windows 11, results were presented in simple measures of frequency, percentage, mean, range and standard deviation and illustrated as tablets and figures.

TABLE 1. Demographic and clinical characteristics of the study sample (n=100)

Variable	Missed Miscarriage (n=50)	Viable Pregnancy (n=50)	p-value
Maternal age (years)			
<20	4 (8%)	3 (6%)	0.365
20–24	7 (14%)	8 (16%)	
25–29	15 (30%)	16 (32%)	
30–34	14 (28%)	15 (30%)	
35–39	6 (12%)	5 (10%)	
≥40	4 (8%)	3 (6%)	
mean ± SD	30.2 ± 5.4	28.9 ± 6.1	
Gestational age (weeks)			
mean ± SD	9.2 ± 1.8	8.1 ± 1.3	0.185
Parity			
Multiparous	38 (76%)	41 (82%)	0.107
Nulliparous	12 (24%)	9 (18%)	
Previous miscarriage			
Yes	16 (32%)	8 (16%)	0.273
No	34 (68%)	42 (84%)	

TABLE 2: Comparison of serum Ang-1 levels between missed miscarriage and viable pregnancy groups

Serum Ang-1 (pg/mL)			
Group	Mean ± SD	Range	p-value
Missed Miscarriage	635.7 ± 119.9	435.9 – 797.8	<0.001
Viable Pregnancy	977.1 ± 320.59	700 – 1620.3	

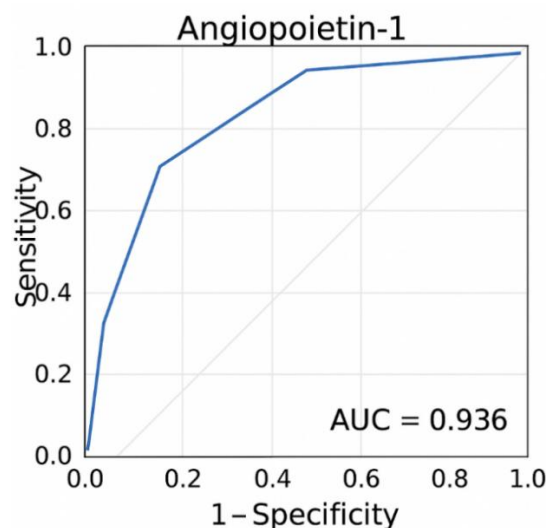


Figure 1: ROC analysis of serum Ang-1 in differentiation missed miscarriage from viable intrauterine pregnancy.

The independent samples t-test was used to compare mean serum (Ang-1 levels and other continuous variables between the two groups (missed miscarriage vs. viable pregnancy). The Chi-square test (χ^2) was used to analyses associations between categorical variables. A p-value < 0.05 was considered statistically significant.

Receiver operating characteristic (ROC) curve was used to evaluate the diagnostic performance of serum Ang-1 in predicting missed miscarriage, and the area under the curve (AUC) was calculated. The optimal cut-off value and sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using Youden's index.

III. RESULTS

The current study included 100 patients divided to two groups 50 women diagnosed with missed miscarriage in the first trimester and 50 women with viable first-trimester pregnancies (Control group).

the mean maternal age among women with missed miscarriage was 30.2 ± 5.4 years and 28.9 ± 6.1 years among women with viable pregnancy. Although the mean age was higher in the missed miscarriage group, the difference was not statistically significant.

The mean gestational age at presentation was 9.2 ± 1.8 weeks in the missed miscarriage group and 8.1 ± 1.3 weeks in the viable pregnancy group. [This difference not statistically significant ($p = 0.185$)].

Among women with a missed miscarriage, 76% were multiparous and 24% were nulliparous, compared with 82% multiparous and 18% nulliparous among women with a viable pregnancy; this difference was not statistically significant ($P = 0.107$).

A previous history of miscarriage was found in 32% of women with missed miscarriage compared to 16% among those with viable pregnancy, this difference was not statistically significant ($p = 0.273$).

The mean serum Ang-1 level was significantly lower in women with missed miscarriage (635.7 ± 119.9 pg/mL; range 435.9–797.8 pg/mL) compared with those with viable pregnancies (977.1 ± 220.6 pg/mL; range 700–1020.3 pg/mL), and the difference was highly statistically significant ($p < 0.001$). As shown in table 2.

The ROC analysis showed that a serum Ang-1 cut-off value of ≤ 780 pg/mL best discriminated missed miscarriage from viable pregnancy. At this cut off point, sensitivity was 63.6% and specificity was 97.9%. The positive predictive value was 87.5%, while the negative predictive value was 90%. The area under the ROC curve (AUC) was 0.936, indicating excellent diagnostic performance, and the overall diagnostic accuracy was 86%. As in figure 1.

Maternal age showed weak negative correlation with Ang-1 levels ($r = -0.018$), which was not statistically significant ($p = 0.707$).

Gestational age showed statistically significant positive correlation with Ang-1 ($r = 0.268$, $p = 0.038$), suggesting that Ang-1 levels tended to increase slightly as pregnancy progressed.

Parity showed a weak positive correlation ($r = 0.136$) with no statistical significance ($p = 0.811$).

IV. DISCUSSION

The current study investigated the association between maternal serum Ang-1 levels and missed miscarriage in the

first trimester of pregnancy. The mean age of women with missed miscarriage was 30.2 ± 5.4 years compared with 28.9 ± 6.1 years in women with viable pregnancies, with no statistically significant difference. Although several studies show that maternal age is a significant risk factor for missed miscarriage. For instant (Magnus *et al.*, 2019) study on total of 421,201 pregnancies show that the lowest miscarriage risk, at 10%, was observed among women aged 25–29 years, after which the risk increased sharply beyond 30 years of age, reaching 53% in women aged 45 years and older.

A study by (Devall and coomarasamy, 2020) That included 100 women, equally divided into two groups: a case group of women with missed miscarriage and a control group of age- and gestational age-matched women with viable pregnancies also showed that the mean Ang-1 level was significantly lower in the missed miscarriage group compared with the control group (840 ± 174 vs 1157 ± 89 , $P < 0.0001$). Using a cut-off value of $\leq 1,085$ pg/mL, Ang-1 predicted missed miscarriage with a sensitivity of 88% and a specificity of 84%.

The finding across different populations and laboratory settings strengthens the evidence that Ang-1 deficiency is a characteristic biochemical feature of missed miscarriage.

Another study in Al-Yarmouk teaching hospital by (Al Bayati *et al.*, 2022) That included 100 pregnant also showed that the mean Ang-1 level was significantly lower in the missed miscarriage group than in the control group (771.12 ± 165 vs. 1381.12 ± 340.36 ; $P = 0.001$). They concluded that reduced serum Ang-1 levels are strongly associated with missed miscarriage compared with normal viable pregnancies of similar gestational age.

Ang-1 plays a central role in vascular stabilization, endothelial cell survival, and maturation of the placental microvasculature through activation of the Tie-2 receptor. During early pregnancy, proper trophoblastic invasion and spiral artery remodeling depend on balanced angiogenic Signaling.

The current study found significant positive correlation between serum Ang-1 and gestational age, other study variables like maternal age and parity were not significant. This is consistent with (Abozeid *et al.*, 2021) study on 80 pregnant women at 6–8 weeks of gestation that also found no correlation between Ang-1 and age and parity. The mean $\pm$ SD of serum Ang-1 were 926.16 ± 211.48 ($700 - 1620.3$) pg/ml in normal pregnant women, and 700.04 ± 87.87 ($435.9-797.8$) pg/ml in women with missed miscarriage. The cutoff point was ≤ 780.99 pg/ml with high sensitivity and specificity (87.5.% and 90.00% respectively).

The study receiver operating characteristic curve analysis further confirmed the diagnostic utility of Ang-1 in differentiating missed miscarriage from viable pregnancy. A cut-off value of ≤ 780 pg/mL yielded a sensitivity of 63.6%, a specificity of 97.9%, a positive predictive value of 87.5%, a negative predictive value of 90%, and an area under the curve of 0.936, indicating excellent overall diagnostic performance. The very high specificity observed in this study suggests that Ang-1 levels above this cut off can exclude missed miscarriage.

The variation in reported cut-off values between studies may be caused by differences in laboratory kits and calibration.

(Hegazy *et al.*, 2021) study in Egypt also show similar findings were women with missed miscarriage had markedly lower serum Ang-1 levels compared with the control group (700.04 ± 87.87 vs. 926.16 ± 211.48 pg/mL). At a cut-off value of ≤ 780.99 pg/mL, Ang-1 demonstrated 87.5% sensitivity and 90.0% specificity. They concluded that Ang-1 levels are significantly reduced in missed miscarriage as early as 6–8 weeks of gestation, supporting its possible role in the pathogenesis of missed miscarriage; however, Ang-1 alone is not sufficient for immediate diagnosis, and confirmation with transvaginal ultrasound and follow-up remains necessary.

Another study by (Masood *et al.*, 2020) In Kirkuk evaluated serum Ang1 and Ang2 levels showed that Ang1 levels were significantly lower in women with missed miscarriage than in controls (2.92 ± 2.4 vs. 5.6 ± 3.2 ng/mL; $P < 0.05$). Ang2 levels were also significantly reduced in the missed miscarriage group compared with controls (8.12 ± 3.5 vs. 16.81 ± 12.3 ng/mL). They concluded that decreased serum levels of Ang1 and Ang2 are associated with missed miscarriage and may serve as early and effective biomarkers for its diagnosis.

On the other hand, (Schneuer *et al.*, 2014) Study that evaluated serum angiopoietin 1 (Ang-1) and angiopoietin 2 (Ang-2) levels and Ang-1/Ang-2 ratio in 4,785 women concluded that while high Ang-1/Ang-2 ratio is associated with adverse pregnancy outcomes.

The current study also agree with (Rao *et al.*, 2018) Study found that women with missed miscarriage had significantly lower serum angiopoietin 1 levels compared to those with normal viable pregnancies (780.50 ± 134.30 vs. 1102.50 ± 112.40 ; $p = 0.001$). and concluded that reduced serum angiopoietin 1 is associated with missed miscarriage.

V. CONCLUSIONS

Maternal serum Ang-1 levels was significantly lower in women with first-trimester missed miscarriage compared with women with viable pregnancies.

Maternal serum Ang 1 have positive correlation with gestational age, weak positive with parity and negative correlation with maternal age, P value not significant.

Using cutoff value ≤ 780 pg/ml, maternal serum Ang 1 have sensitivity 63.6% specificity 97.9%, AUC 0,963 and overall diagnostic accuracy was 86%.

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