

Association Between TNF Alfa and Recurrent Miscarriage in First Trimester of Pregnancy

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Abstract— Miscarriage is defined as the occurrence of two or more consecutive pregnancy losses before 24 weeks of gestation associated with change in maternal immune responses, particularly an excess of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukins. Elevated TNF- α may impair trophoblast invasion, disrupt placentation, and contribute to recurrent miscarriage. This study aimed to evaluate the possible association between TNF alpha and recurrent miscarriage in the 1st trimester of pregnancy. Case-control study was conducted at Babil Teaching Hospital of Maternity and Children, Iraq, over 10-month period from November 2024 to August 2025. The study included 96 women: 48 with first-trimester missed miscarriage and a history of at least two prior miscarriages (case group), and 48 with viable first-trimester pregnancies without previous miscarriage history (control group). Sociodemographic data, obstetric history, medical history, history of consanguinity, abdominal and pelvic examination of case group and control group, body mass index were recorded. Serum TNF- α levels were measured and compared between groups. Serum TNF- α levels were significantly higher in the miscarriage group (18.1 ± 2.8 pg/mL) than in controls (9.7 ± 1.6 pg/mL, $p < 0.001$). receiver operating characteristic analysis demonstrated excellent discriminative ability, with an area under the curve of 0.91. The optimal cut-off value of 13.5 pg/mL. Sensitivity of 87.5%, specificity of 85.4%, positive predictive value of 84%, negative predictive value of 88.5%, and overall diagnostic accuracy of 86.5%. Women with first trimester miscarriage and a history of recurrent miscarriage show significantly elevated TNF- α levels compared with women with viable pregnancies. TNF- α demonstrated strong diagnostic benefit, suggesting its potential role as an early biomarker for miscarriage risk.

Keywords— TNF Alfa, Obstetric, Gynaecological, Miscarriage.

I. INTRODUCTION

Miscarriage is one of the most common complications of pregnancy and remains a major concern in reproductive medicine worldwide. It is generally defined as the = refers to the loss of a pregnancy before 24 weeks. 60-70% of miscarriages occur during the first trimester [Quenby S, *et al.*, 2021]. Spontaneous abortion is the most common complication of early pregnancy, affecting approximately 10% to 15% of clinically diagnosed pregnancies. When early miscarriages that often go unnoticed, known as chemical pregnancies, are included, the estimated rate rises to between 30% and 50% of all pregnancies [Magnus MC, *et al.*, 201]. Most spontaneous abortions occur during the first trimester, particularly before the twelfth week, and the risk of spontaneous abortion decreases significantly once fetal heart activity is confirmed by ultrasound [Jauniaux E, *et al.*, 2018]. Recurrent abortion, also referred to as recurrent pregnancy loss, is defined as the loss of two or more consecutive pregnancies before the fetus reaches viability outside the uterus. In addition to its physical consequences, recurrent abortion places a significant psychological, social, and economic burden on affected women and their families, often leading to anxiety, depression, and emotional distress [Saxena R, *et al.*, 2015].

Recurrent miscarriage is multifactorial, such as Recurrent miscarriage is multifactorial, such as Maternal age, Previous miscarriage, Obesity. Smoking, Alcohol and caffeine intake and chronic medical conditions such as diabetes mellitus, renal disease, hypertension and cardiac disease, Infections, Over distended uterus (multiple pregnancy), Uterine or anatomical abnormalities such as congenital anomalies (septate or

bicornuate uterus) or acquired lesions (fibroids distorting the uterine cavity or intrauterine adhesions) [Committee ASRM 2020; Dimitriadis E, *et al.*, 2020]. Cervical insufficiency can also contribute to pregnancy loss, Endocrine and hormonal disorders including luteal phase defects or low progesterone levels, polycystic ovary syndrome (PCOS), thyroid dysfunction, and hyperprolactinemia. [Larsen EC, *et al.*, 2017], Immunological causes which include autoimmune conditions (antiphospholipid syndrome and systemic lupus erythematosus) and alloimmune mechanisms whereby an abnormal maternal immune tolerance of fetal antigens can lead to miscarriage. Certain cytokine imbalances, such as elevated TNF- α or IL-6, have also been identified. [Devall AJ, *et al.*, 2019; Christiansen OB, 2019], Inherited and acquired thrombophilias (Factor V Leiden mutation, prothrombin gene mutation, antithrombin III, protein C, and protein S deficiencies, and antiphospholipid syndrome) are known contributors. [Wang X, *et al.*, 2022], Drugs and medication use: Exposure to teratogenic drugs such as isotretinoin, methotrexate, antiepileptics, warfarin, some chemotherapeutic agents, and illicit drugs may significantly increase the risk of miscarriage through direct embryotoxic and placental effects. [Saito S, *et al.*, 2017; Yamada H, *et al.*, 2020], Genetic and chromosomal abnormalities such as parental chromosomal translocations (for example, a balanced translocation) and sporadic embryonic aneuploidies. [Chen H, *et al.*, 2023] and Ethnicity some ethnic background is considered a risk factor for miscarriage [Zhao X, *et al.*, 2021; Raghupathy R, 2018].

Successful pregnancy requires a delicate balance between maternal immune tolerance toward the semi-allogeneic fetus and the controlled inflammatory responses necessary for implantation and placental development. Cytokines are key

mediators of these immune processes and play crucial roles throughout gestation. Among them, Tumor Necrosis Factor- α (TNF- α) has emerged as one of the most important pro-inflammatory cytokines involved in reproductive immunology. TNF- α is primarily produced by activated macrophages, T lymphocytes, and natural killer cells, and contributes to inflammation, angiogenesis, tissue remodeling, and immune regulation during early pregnancy [Ford HB, *et al.* 2016; Metwally M, *et al.* 2016].

Although physiological levels of TNF- α are essential for normal implantation and placental formation, excessive production of this cytokine may adversely affect pregnancy outcomes. Elevated TNF- α levels have been associated with impaired trophoblast invasion, increased trophoblast apoptosis, endothelial dysfunction, reduced uteroplacental blood flow, and disruption of maternal-fetal immune tolerance [Pineles BL, *et al.* 2018]. These pathological effects may contribute to implantation failure and recurrent pregnancy loss. Several studies have demonstrated significantly higher serum and decidual TNF- α levels in women with recurrent miscarriage compared with healthy pregnant controls. Therefore, evaluating the association between TNF- α and recurrent miscarriage may enhance understanding of the underlying immunological mechanisms and support the development of novel biomarkers and targeted therapeutic approaches for women at increased risk of pregnancy loss.

II. METHODS

Study Design

Prospective case-control study designed to evaluate the association between serum tumor necrosis factor- α (TNF- α) levels and recurrent miscarriage in the first trimester of pregnancy.

Study Setting

The study was conducted at Babil Teaching Hospital of Maternity and Children in emergency unit over a period of 10 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. A total of 96 women in the first trimester of pregnancy were recruited and divided into two groups:

- Case group (n = 48): Women presenting with first trimester missed miscarriage (≤ 13 weeks gestation) and had history of previous ≥ 2 miscarriage confirmed by ultrasound evidence of absent fetal cardiac activity with a closed cervical os and retained products of conception.
- Control group (n = 48): Women with ongoing viable first-trimester pregnancies without history of previous miscarriage.

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.

3. Data and information of the participants were kept confidential.

Administrative approvals were granted from Babil Teaching Hospital of Maternity and Children.

Inclusion Criteria

1. women aged 18 to 40 years.
2. confirmed intrauterine pregnancy with gestational age ≤ 13 weeks.
3. For the case group: Women presenting with symptoms suggestive of early pregnancy loss (e.g., mild vaginal bleeding or lower abdominal pain) and subsequently diagnosed with first trimester missed miscarriage by ultrasound.
4. For the control group: Women with ongoing viable intrauterine pregnancies in first trimester and no previous history of miscarriage.

Exclusion Criteria

1. Autoimmune or inflammatory disorders (e.g., systemic lupus erythematosus, rheumatoid arthritis)
2. Chronic systemic diseases (diabetes, hypertension, liver or kidney disease)
3. Uterine anomalies (septate or bicornuate uterus)
4. Acute infection or fever at the time of presentation.
5. Chronic use of medications (e.g. isotretinoin, methotrexate)
6. Endocrine disorders (thyroid, pituitary and adrenal)

Data Collection

A paper form questionnaire was used to collect relevant data for each participant after obtaining verbal consent. The questionnaire was filled by the researcher and included:

- Sociodemographic Data: Age, residence (urban/rural), and parity
- Medical and Obstetric History: Previous miscarriages, live births, history of chronic illnesses, and gestational age at presentation
- Physical Examination and Clinical Assessment:
 - General Clinical Assessment: Systemic examination to detect signs of illness, anemia, or infection
 - PV exam for cervical status.
 - Anthropometric Measurements:
 - Height: Measured in centimeters with the participant barefoot, using a wall-mounted stadiometer
 - Weight: Measured in kilograms using a calibrated digital scale
 - Body Mass Index (BMI): Calculated as weight (kg) / height (m^2)
- Ultrasound Assessment:
 - Transvaginal or transabdominal ultrasound, using SAMSUNG USS-HS6NL40/WR(korea, 2021) was done by senior radiologist at the hospital to all the participants. with transvaginal ultrasound frequency 5.9MHz
 - Transabdominal ultrasound frequency 2.5MHz
 - In the case group: Ultrasound findings confirmed missed miscarriage.
 - In the control group: Ultrasound confirmed a viable intrauterine pregnancy with positive cardiac activity.

Laboratory measurements

A venous blood sample (5ml) was collected by laboratory personal from each participant into plain tube. Sample were allowed to clot at room temperature, and serum was separated by centrifugation at 3000 rpm for 10 minutes. The serum was aliquoted and stored at -20 °c until analysis.

Serum TNF- α levels were measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit Elabscience® Human TNF- α (Tumor Necrosis Factor Alpha) ELISA Kit, following the manufacturer's protocol.

Statistical Analysis

Data analysis was done using IBM® 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.

Associations were tested using the independent samples t-test for continues variables and chi-square test or fisher's exact test for associations between categorical variables. A p-value < 0.05 was considered statistically significant.

Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of TNF- α in differentiating miscarriage from viable intrauterine pregnancy. The area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for different TNF- α cut-off levels.

III. RESULTS

The current study included 96 women, with 48 participants in the case group and 48 participants in the control group. Regarding age distribution the mean age was 27.8 $\pm$ 5.6 years in the case group and 28.2 $\pm$ 5.1 years in the control group. Most women in cases group were in 25-29 age group. There was no statistically significant difference in age distribution between the groups (p = 0.281). Regarding residence, 30 women (62.5%) in the case group and 25 women (52.1%) in the control group lived in urban areas, while 18 (37.5%) in the case group and 23 (47.9%) in the control group lived in rural areas. The difference in residence between the groups was not statistically significant (p = 0.147).

TABLE 3.1: Sociodemographic characteristics of participants

Variable	Case group (n=48)	Control group (n=48)	p-value
Age (years)			
18–24	4 (8.3%)	10 (20.8%)	0.281*
25–29	20 (41.7%)	14 (29.2%)	
30–34	14 (29.2%)	13 (27.1%)	
35–40	10 (20.8%)	11 (22.9%)	
Mean ± SD	27.8 ± 5.6	28.2 ± 5.1	
Residence			
Urban	30 (62.5%)	25 (52.1%)	0.147*
Rural	18 (37.5%)	23 (47.9%)	
Parity			
Nulliparous	12 (25%)	8 (16.7%)	0.319*
Multiparous	36 (75%)	40 (83.3%)	

In the case group Twelve women (25%) and 8 women (16.7%) in the control group were nulliparous, while 36 women (75%) in the case group and 40 women (83.3%) in the control group were multiparous. Parity distribution did not differ significantly between the groups (p = 0.319). as shown in table 3.1.

The mean gestational age at presentation was 10.1 $\pm$ 1.2 weeks in the case group and 11.2 $\pm$ 1.1 weeks in the control group, with no significant difference between the groups (p = 0.217).

The mean number of live births was significantly lower in the case group (1.9 $\pm$ 0.7) compared to the control group (2.8 $\pm$ 0.9) (p < 0.001).

The mean BMI was 29.7 $\pm$ 3.8 kg/m² in the case group and 27.3 $\pm$ 3.2 kg/m² in the control group, with no statistically significant difference (p = 0.131). as shown in table 3.2.

TABLE 3.2: Obstetric history and anthropometric measurements.

Variable	Case group (n=48)	Control group (n=48)	p-value
Gestational age at presentation (weeks, mean $\pm$ SD)	10.1 $\pm$ 1.2	11.2 $\pm$ 1.1	0.217
Live births (mean $\pm$ SD)	1.9 $\pm$ 0.7	2.8 $\pm$ 0.9	<0.001
BMI (kg/m ²)			0.131
18.5-24.9 (Normal)	14 (29.2%)	22 (45.8%)	
25-29.9 (Overweight)	19 (39.6%)	18 (37.5%)	
Mean $\pm$ SD	29.7 $\pm$ 3.8	27.3 $\pm$ 3.2	

Serum TNF- α levels were significantly higher in the case group compared to the control group (Figure 3.1). The mean TNF- α level in the case group was 18.1 $\pm$ 2.8 pg/mL, ranging from 12.8 to 23.5 pg/mL, whereas the control group the mean TNF- α level was 9.7 $\pm$ 1.6 pg/mL, ranging from 7.5 to 12.3 pg/mL. This difference was highly statistically significant (p < 0.001) as shown in table 3.3.

TABLE 3.3: Serum TNF- α levels

TNF- α (pg/mL)	Case group	Control group	p-value
Mean	18.1	9.7	<0.001
$\pm$ SD	2.8	1.6	
Range	12.8-23.5	7.5-12.3	

IV. DISCUSSION

In this study of 96 women 48 in the case group with first-trimester miscarriage + history of previous miscarriage and 48 in the control group with ongoing viable pregnancies. The case and control groups were comparable in age, gestational age, BMI, residence, and parity for good baseline matching and to reduce bias.

In contrast, significant differences were observed in obstetric history. Women in the case group presented had fewer live births because all had a history of previous miscarriages which reduce reproductive success and parity.

The current study results show that the mean serum tumor necrosis factor-alpha (TNF- α) levels were significantly higher in the case group (18.1 $\pm$ 2.8 pg/ml) versus the control group (9.7 $\pm$ 1.6 pg/ml), p < 0.001. TNF- α at a cut-off of 13.5 pg/ml had excellent discriminative ability (AUC = 0.91) with sensitivity ~87.5% and specificity ~85.4%.

The current study finding of significantly elevated TNF- α in miscarriage cases aligns with previous literature suggesting a pro-inflammatory shift (Th1 dominance) is implicated in early pregnancy loss. For example, [Zammiti, *et al.* 2008]. Reported that heightened maternal serum TNF- α was associated with idiopathic recurrent pregnancy loss (RPL)

Another a review by Li *et al.* Described how TNF- α , because of its ability to induce trophoblast apoptosis and impair placentation, may have a mechanistic role in RPL [Li HH, *et al.* 2016].

In Iraq a study by [Nadia Al-Hilli, 2009]. examined whether TNF- α is linked to miscarriage by measuring serum levels in 35 women: 15 with recurrent miscarriage, 10 with missed miscarriage, and 10 with normal first-trimester pregnancies. found that TNF- α levels were markedly elevated in both miscarriage groups compared with healthy controls. Women with recurrent miscarriage had the highest concentrations (68.94 pg/mL), followed by those with missed miscarriage (54.39 pg/mL), while the control group showed much lower levels (27.40 pg/mL). Although TNF- α was higher in recurrent than in missed miscarriage, the difference between these two groups was not statistically significant. She concluded that there is a strong association between elevated TNF- α and both recurrent and missed miscarriage.

Another study by [Ali, *et al.* 2011]. The study aimed to assess serum levels of TNF- α and IL-6 in Iraqi women experiencing first-trimester missed or threatened miscarriage and compare them with levels in normal pregnancies in Al-Yarmouk Teaching Hospital including 62 women in early pregnancy 18 with threatened miscarriage, 22 with missed miscarriage and 22 healthy pregnant women and an additional 23 non-pregnant women found that TNF- α levels were markedly elevated in women with missed miscarriage, with mean values significantly higher than those in both the threatened miscarriage group and the non-pregnant controls (17.68 ± 2.90 pg/ml vs. 9.75 ± 1.66 pg/ml and 4.41 ± 1.23 pg/ml). They suggest that elevated TNF- α may contribute to the pathophysiology of missed and threatened miscarriage.

The AUC in the current study was 0.91 and ROC analysis suggest that TNF- α may be a useful biomarker for distinguishing women at risk of miscarriage (in the first trimester) from those with viable pregnancies.

A meta-analysis including 1,371 women by [Zhang, *et al.* 2016]. Found that baseline TNF- α concentrations were significantly higher in women with recurrent spontaneous miscarriage compared with healthy controls. The pooled standardized mean difference was 2.82 (95% CI: 1.57–4.06), with a highly significant overall effect ($P < 0.0001$). They concluded that women with recurrent miscarriage have markedly elevated serum TNF- α levels. This reinforces the role of TNF- α as an important immune-related factor in the pathogenesis of recurrent spontaneous miscarriage.

In contrast to our finding, the study conducted by [Kwiatkowska, *et al.* 2021]. reported that TNF- α levels showed only a slight decrease in the miscarriage group and did not appear to play a distinguishing role in the systemic immune response of women with missed miscarriage compared to normal pregnancies.

The immunological environment of early pregnancy is characterised by a delicate balance between immune tolerance and pro-inflammatory signaling. Maternal adaptation requires suppression of excessive Th1-type cytokines; however, elevated TNF- α tilts the balance towards inflammation, which may impair trophoblast invasion, damage the decidual interface, trigger apoptosis of placental cells, or activate complement/coagulation cascades at the maternal-fetal interface.

The current study finding of elevated TNF- α suggest that high TNF- α levels may reflect or cause impaired implantation or early placental development leading to early pregnancy failure. A study by Mu *et al.* on total of 121 patients assessed whether adding TNF- α inhibitors (TNFi) to standard heparin therapy improves pregnancy outcomes in women with unexplained recurrent miscarriage found that TNFi treatment substantially improved outcomes. Women receiving TNFi achieved a significantly higher 24-week live birth rate (71.2% vs. 50.9%) and a notably lower miscarriage rate (24.2% vs. 43.6%) compared with controls. Also supporting that TNF- α -related inflammation may play a more pronounced role in recurrent miscarriage [Wu H, *et al.* 2021].

[Piosik, *et al.* 2021] study also found that TNF- α concentrations increased as pregnancy progressed and were consistently higher in women who had previously carried a pregnancy to term before experiencing miscarriage, compared with women experiencing miscarriage for the first time.

V. CONCLUSIONS

Women who experienced miscarriage and had a history of recurrent miscarriage showed significantly higher serum TNF- α levels compared to women with viable pregnancies and no miscarriage history.

The area under the curve (AUC) was 0.91, indicating excellent discriminative ability at optimal cut-off value of 13.5 pg/mL, sensitivity was 87.5%, specificity of 85.4%, positive predictive value 84%, negative predictive value 88.5%, and the overall diagnostic accuracy was 86.5%).

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