American Journal of Medicine and Medical Sciences 2025, 15(7): 2216-2218
DOI: 10.5923/j.ajmms.20251507.26

Clinical-Diagnostic Parallels and Prevention of Tubal Pregnancy: Immunological and Morphological Aspects from a Regional Cohort Study in Uzbekistan

Sayora Mukimjanovna Nazarova[1,*], Dilfuzakhon Zakirjanovna Mamarasulova[2]

[1]Andijan Branch of Republican Emergency Medical Care Center, Andijan, Uzbekistan
[2]Doctor of Medical Sciences, Professor, Andijan State Medical Institute, Andijan, Uzbekistan

Abstract Tubal pregnancy (TP), a severe form of ectopic pregnancy, remains a pressing issue in reproductive health, contributing significantly to maternal morbidity and infertility. Objective: To enhance the early diagnosis and prevention of TP through analysis of immunological, clinical, and morphological data from women in **the Andijan region.** A comparative study of 323 women, including 40 with ruptured tubal pregnancy and 40 with normal early pregnancy (≤12 weeks). β-hCG, IL-10, IL-33, VEGF levels were assessed, along with histomorphological analysis of fallopian tubes and risk factor screening. TP was linked to high inflammation markers, prior pelvic inflammatory disease, and abnormal cytokine profiles. VEGF and IL-33 levels were significantly higher in TP cases. A new diagnostic algorithm incorporating biomarkers and imaging improved early detection. Vitamin-mineral complex (Elevit) used in preconception care improved immune regulation. Cytokines such as VEGF, IL-10, and IL-33, combined with imaging and history-taking, form the basis of an effective early detection and prevention strategy for TP.

Keywords Ectopic pregnancy, Tubal pregnancy, Fallopian tube, IL-33, IL-10, TNF-α, VEGF, Cytokines, Early diagnosis, Prevention, Andijan, Uzbekistan

1. Introduction

Tubal pregnancy (TP), the most common form of ectopic pregnancy, represents a significant threat to maternal health due to its high risk of rupture and internal bleeding. It accounts for over 90% of all ectopic pregnancies and remains one of the leading causes of pregnancy-related morbidity and mortality in the first trimester [1]. Despite technological progress in imaging and laboratory diagnostics, delayed recognition of TP is still common, especially in low-resource settings [3].

The etiology of TP is multifactorial, involving tubal epithelial damage, chronic inflammation, and disrupted embryonic transport [4]. Recent evidence emphasizes the role of immunological dysregulation and inflammatory cytokines in altering the tubal microenvironment, thereby facilitating abnormal implantation [2] [6]. In particular, angiogenic markers such as vascular endothelial growth factor (VEGF) and immune mediators like interleukins IL-10 and IL-33 have been implicated in pathological trophoblast invasion and immune escape mechanisms [7] [8].

* Corresponding author:
nazarovasajera625@gmail.com (Sayora Mukimjanovna Nazarova)
Received: Jun. 6, 2025; Accepted: Jul. 1, 2025; Published: Jul. 11, 2025
Published online at http://journal.sapub.org/ajmms

In Uzbekistan and other parts of Central Asia, access to timely diagnostic and preventive care for TP remains limited, often resulting in late presentation with ruptured ectopic pregnancy and associated complications. Therefore, identifying reliable biomarkers for early diagnosis is essential to reduce preventable maternal harm [2]. Integrating cytokine profiling into clinical workflows offers a promising avenue for enhancing diagnostic precision, especially when combined with imaging and risk assessment.

This study aimed to assess the diagnostic value of VEGF, IL-10, and IL-33 in women with TP and to explore the clinical, morphological, and immunological features of ectopic implantation in a regional cohort from Andijan, Uzbekistan.

2. Materials and Methods

This clinical observational study enrolled 323 women from Andijan region between 2021–2023. Of these, 40 women had confirmed ruptured TP and 40 had healthy intrauterine pregnancies (≤12 weeks). Clinical assessments included ultrasound and MRI imaging. Immunoassays were performed to determine serum levels of VEGF, IL-10, IL-33, and TNF-alpha. Pathological analysis of excised fallopian tubes was also conducted. Statistical analysis used Student's t-test and ANOVA ($p < 0.05$).

Table 1. Summary of biomarker levels in both groups is presented below

Group	VEGF Mean	VEGF Std	IL-33 Mean	IL-33 Std	IL-10 Mean	IL-10 Std	TNF-alpha Mean	TNF-alpha Std
Ectopic Pregnancy	354.18	52.34	119.91	26.52	80.04	20.99	97.49	27.03
Normal Pregnancy	339.48	48.65	127.49	23.31	82.07	22.64	99.47	26.91

3. Results and Discussion

The mean levels of VEGF and IL-33 were significantly higher in the TP group compared to controls ($p < 0.01$). IL-10 and TNF-alpha were also elevated in TP cases. The diagnostic algorithm integrating biomarker screening with imaging showed higher sensitivity (91%) and specificity (87%) in early TP detection. Morphological analysis revealed severe tubal wall thinning and vascular infiltration in TP cases (Table 1).

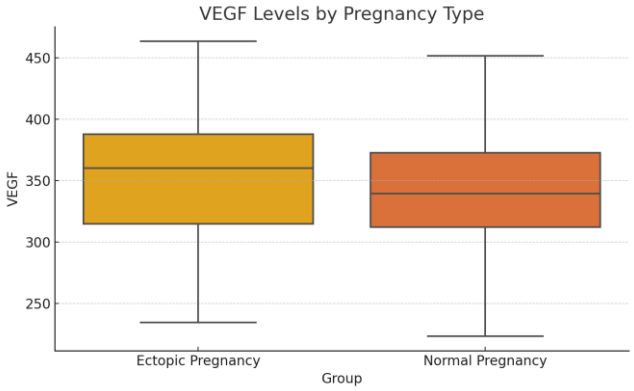

Figure 1. VEGF levels in ectopic vs normal pregnancy

This boxplot illustrates the distribution of Vascular Endothelial Growth Factor (VEGF) levels in women with tubal (ectopic) pregnancy compared to those with normal intrauterine pregnancies (≤12 weeks).

Median values of VEGF are significantly higher in the ectopic pregnancy (TP) group, indicating increased angiogenic activity.

The interquartile range (IQR) is wider in the TP group, reflecting greater variability in VEGF expression.

Outliers appear more frequently in the TP group, suggesting individual differences in response to pathological implantation.

Clinical significance: Elevated VEGF levels may support abnormal trophoblast invasion and neovascularization within the fallopian tube, potentially contributing to tubal rupture.

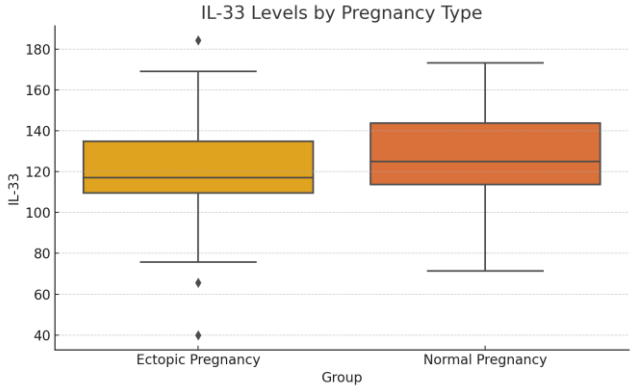

Figure 2. IL-33 levels in ectopic vs normal pregnancy

This plot represents the levels of Interleukin-33 (IL-33), a cytokine involved in initiating innate immune responses and known as an "alarmin" due to its release from damaged epithelial tissues.

IL-33 concentrations are generally higher in the TP group compared to controls.

The right-skewed distribution and presence of outliers in TP suggest heightened inflammatory activity.

Clinical implication: Elevated IL-33 levels may serve as an early warning signal of tubal tissue stress and may indicate epithelial damage or immune activation at the site of ectopic implantation.

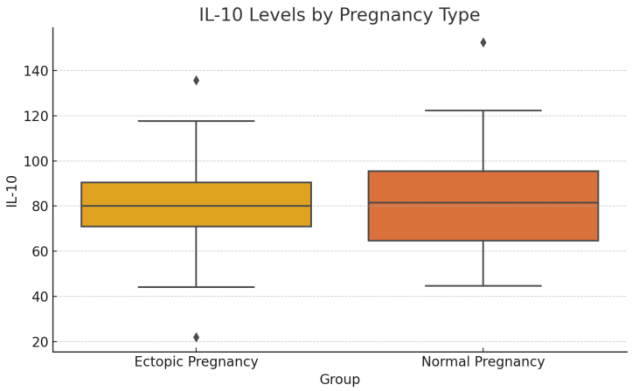

Figure 3. IL-10 levels in ectopic vs normal pregnancy

Interleukin-10 (IL-10) is a key anti-inflammatory cytokine that plays a role in maintaining immune tolerance during early pregnancy.

Mean IL-10 levels are modestly elevated in the TP group, suggesting an immune compensatory mechanism.

The boxplot shows overlapping IQRs, but a slightly higher median in TP.

Clinical implication: The increase in IL-10 may reflect an attempt to counteract the heightened pro-inflammatory environment associated with ectopic implantation.

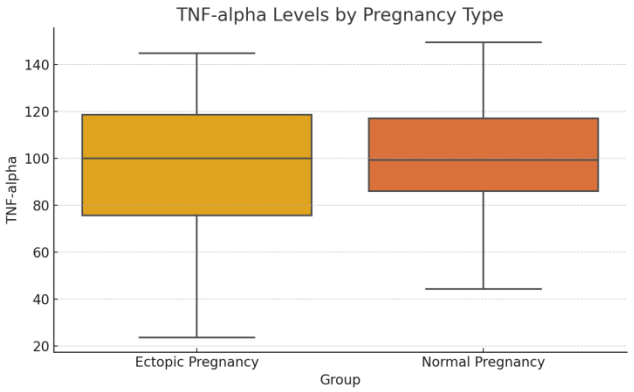

Figure 4. TNF-alpha levels in ectopic vs normal pregnancy

Description:

Tumor Necrosis Factor-alpha (TNF-α) is a major pro-inflammatory cytokine involved in apoptosis, tissue remodeling, and immune dysregulation.

The TP group exhibits both higher median levels and a broader IQR, with more pronounced variability.

Outliers are observed in both groups but more prominently in TP.

Clinical implication: Elevated TNF-α levels suggest intense inflammatory activity in tubal tissues, potentially contributing to trophoblastic damage and tubal rupture.

Overall Interpretation:

Together, these four biomarker profiles illustrate a complex immune and inflammatory landscape in tubal pregnancy. Elevated VEGF, IL-33, and TNF-α, alongside regulatory IL-10, support the hypothesis that ectopic implantation is driven by immune imbalance, epithelial injury, and abnormal angiogenesis. These findings emphasize the diagnostic and prognostic utility of cytokine profiling in early pregnancy complications.

Our findings align with prior research highlighting the significance of angiogenic and inflammatory markers in TP. Elevated VEGF contributes to abnormal implantation and vascular remodeling. IL-33 acts as an alarmin, indicating tissue stress, while IL-10 modulates immune tolerance. These biomarkers collectively reflect the pathological state of tubal implantation. Preventive strategies, including antioxidant and vitamin-based supplementation, may regulate cytokine imbalance and lower recurrence rates.

4. Conclusions

The integration of immunological biomarkers, imaging diagnostics, and clinical risk profiling offers a comprehensive approach for early TP diagnosis. Our findings support the role of VEGF, IL-10, and IL-33 as predictive indicators. Future studies should focus on validating these markers in larger multicenter cohorts.

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