Archives of Advances
in Biosciences

Original Article:

The Role of CA-125 Levels as a Prognostic Indicator for Response to Medical Treatment in Fallopian Ectopic Pregnancy

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Cite this article as: Jayervand, F., Mohamadianamiri, M., Saghafian larijani, S., Kazerooni, M., Shahbazi, A., Pazoki, B., Azizi, S., Jamshidnezhad, N., Mokhtari, K., & Eslami Vaghar, M. (2024). CA-125 level as a prognostic factor for response in medical treatment of fallopian ectopic pregnancy. Archives of Advances in Biosciences, 15(1), 1–11. https://doi.org/10.22037/aab.v15i1.46370

https://journals.sbmu.ac.ir/aab/article/view/46370

Article info:
Received: 04 Oct 2024
Accepted: 23 Nov 2024
Published: 26 Nov 2024

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Abstract

Introduction: Ectopic pregnancy (EP) involves implantation outside the uterus, posing risks of rupture and hemorrhagic shock. Biomarkers like CA-125 have shown potential in predicting EP progression. This study evaluates CA-125's diagnostic and therapeutic value, focusing on its association with complications in medically treated patients.

Materials and Methods: This prospective cohort study included patients diagnosed with ectopic pregnancy (EP) who were deemed eligible for methotrexate treatment and provided informed consent. Serum β-hCG and CA-125 levels were measured on days 1, 4, and 7 of therapy. Participants were closely monitored for complications related to EP that might require surgical intervention, as well as their response to single-dose methotrexate and the progression of β-hCG levels throughout the treatment period. The study further investigated the patterns of CA-125 levels and their potential association with the development of complications and β-hCG trends.

Results: The study included 100 patients with a mean age of 29.8 years. It was found that a portion of patients required a second dose of methotrexate or surgery. Single-dose methotrexate was effective in about half of the cases, while the other half required additional intervention. CA-125 levels were significantly elevated on days 4 and 7 in patients requiring a second dose of methotrexate and on day 1 in those requiring surgery ($P < 0.001$). Elevated CA-125 levels were also consistently observed across all days in patients with treatment failure ($P < 0.001$).

Conclusion: In summary, monitoring serial CA-125 levels in cases of tubal pregnancy offers critical information regarding the risk of gestational sac rupture and assists in evaluating the need for surgical intervention or an additional dose of methotrexate (MTX).

Keywords: Ectopic pregnancy, βhCG, CA-125, MTX

1. Introduction

Ectopic implantation most frequently occurs within the fallopian tube (tubal ectopic pregnancy, TEP), as a result of the embryo's natural transit through the reproductive tract [1,5]. The mechanisms underlying EP remain incompletely understood. Much of the available data is derived from in vitro studies, as EP is uncommon in animal models, making it challenging to establish a suitable experimental framework [6]. It is hypothesized that the movement of the oocyte and subsequently the embryo through the fallopian tube is regulated by three primary factors: ciliary motion, tubal contractility, and tubal fluid dynamics. These processes are influenced by the paracrine interactions between the fallopian tube's epithelium and endothelium, the immune system, and the developing embryo [7].

During the first trimester of pregnancy, extravillous trophoblast (EVT) cells invade the maternal decidua. This invasive activity typically decreases by the second trimester and is restricted to the inner third of the myometrium. In tubal ectopic pregnancy (TEP), the distinct immunological microenvironment impairs apoptosis, resulting in excessive and uncontrolled invasion into the tubal wall. This invasive process may be further aggravated by endometriotic lesions through the activation of the Slit2/Robo1 signaling pathway [8,9]. In a normal pregnancy, the endometrium becomes receptive through the interaction of pro-inflammatory cytokines. Likewise, in the pathophysiology of tubal ectopic pregnancy (TEP), the inflammatory environment and molecular signaling pathways contribute to tubal receptivity, promoting embryo adhesion and invasion, which ultimately results in implantation [10]. Alterations in 17-β-estradiol levels may contribute to the development of various abnormalities, including TEP [11].

A serum biomarker is a molecule produced by an affected individual that signifies a diseased state and can be detected in the serum. An ideal biomarker for EP would facilitate early diagnosis or help predict the prognosis [12].

Diagnosing a tubal ectopic pregnancy at an early stage can be challenging, as nearly one-third of all cases do not present with clinical signs, and 9% of cases remain asymptomatic until rupture occurs [13]. Furthermore, in cases of suspected pregnancy, up to half of the diagnoses cannot be confirmed during the initial consultation, even with ultrasonography and β-hCG measurement, despite advancements in ultrasound resolution [14,15]. As a result, diagnosing tubal ectopic pregnancy can be a time-consuming and expensive process, which not only impacts the patient's psychological well-being but also contributes to increased healthcare costs [16,17]. The Biomarkers Definitions Working Group defines a serum biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." [16]. Given the absence of suitable animal models for tubal ectopic pregnancy, studies on potential biomarkers are predominantly carried out in human subjects. This approach presents significant challenges in interpreting the utility of biomarkers due to small sample sizes, gestational variations, and the inclusion of samples from women with conditions that are difficult to differentiate. Additionally, large prospective studies are rare. Despite these obstacles, the logical approach to biomarker identification from the pre-genomic era has led to the identification of several candidate biomarkers with varying potential. These biomarkers often exhibit common patterns, which may inform the development of novel biomarker identification and serum diagnostic strategies in the post-genomic era [18-29] [Figure 1]. Several markers play crucial roles in the pathophysiology of EP by influencing various biological processes. PROKR1, PROKR2, TNF-α, IL-6, IL-8, and BAFF are highly expressed markers associated with an inflammatory environment, contributing to the abnormal implantation seen in EP. Hormonal regulation is affected by elevated levels of estradiol. In the context of the endocannabinoid system, anandamide is highly expressed, whereas fatty acid amide hydrolase and cannabinoid receptor 1 show low expression levels. Factors involved in migration and implantation include low levels of adrenomedullin and high levels of VEGF and β-catenin, which further underscore their role in the aberrant growth and location of the embryo [30].

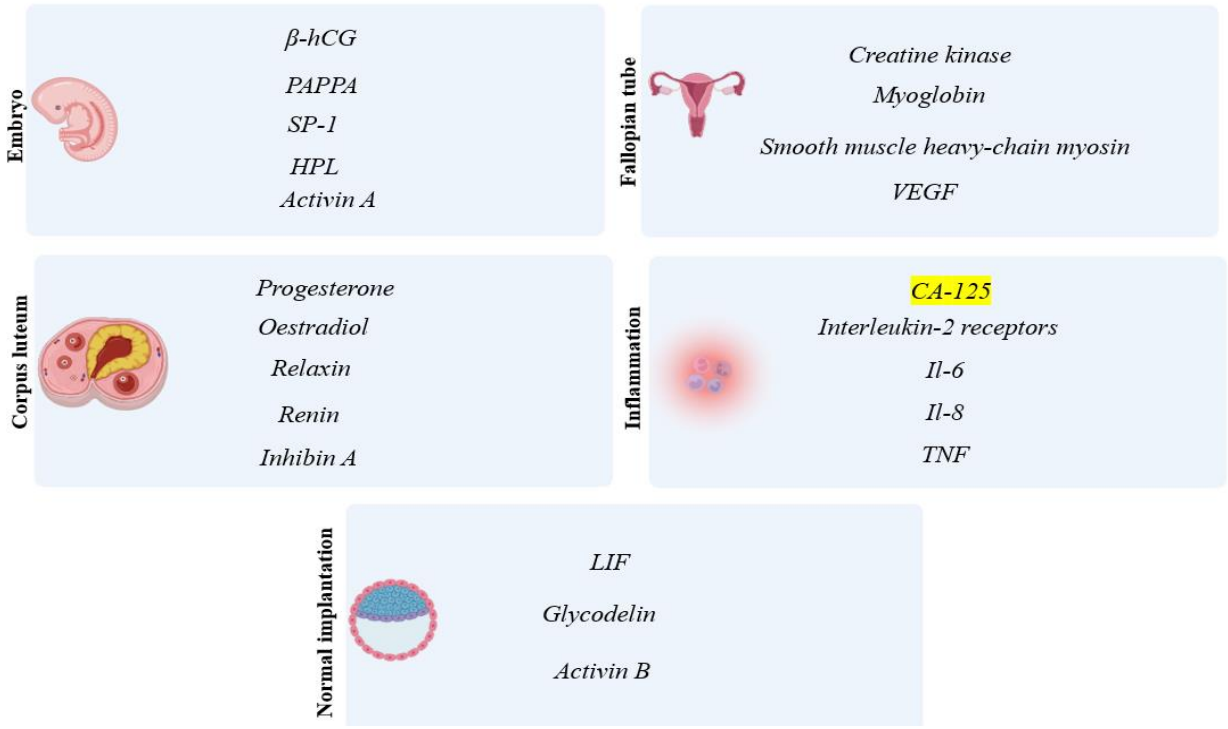

Figure 1. Key markers associated with abnormal trophoblast development, corpus luteum dysfunction, ectopic pregnancy, inflammation, and normal uterine implantation.

β-hCG is commonly used to detect and monitor the progression of pregnancy, as well as to assess the effectiveness of treatment in conditions such as etopic pregnancy[31].

Recent studies highlight the role of CA125 not only as a marker in ovarian cancer but also in other reproductive pathologies, including ectopic pregnancy [32] . Additionally, the levels of CA-125 increase during pregnancy, as it is significantly present in the chorion, amniotic fluid, and maternal decidua [33]. Some studies have indicated that CA-125 levels increase in patients experiencing vaginal bleeding and are at risk of miscarriage. This is believed to be due to the destruction of the maternal decidua, which leads to the release of the marker. Additionally, research has shown that in cases of ruptured ectopic pregnancy, CA-125 levels are significantly higher compared to cases where rupture has not occurred [34]. Therefore, it can be concluded that an increase in CA-125 levels during the monitoring of treatment in this patient group indicates an increased risk of rupture. This can serve as an important warning signal for the healthcare provider managing the patient [35]. Assessing serum levels of progesterone, Beta hCG, and CA 125 during the first trimester provides valuable insights into the viability and overall health of the pregnancy [36].

The schematic representation of CA125 binding to mesothelin and its subsequent role in neoplastic cell migration and metastatic diffusion in advanced serous ovarian carcinoma offers insights into the molecular mechanisms underpinning cell migration and invasion. Similarly, in the context of ectopic pregnancy, elevated CA125 levels could reflect inflammatory processes or tissue remodeling, analogous to tumor metastasis, thereby serving as a prognostic marker for treatment response. Understanding this pathway allows us to draw parallels between the molecular behavior of CA125 in ovarian cancer and its potential implications in the prognosis and management of ectopic pregnancies [Figure 2].

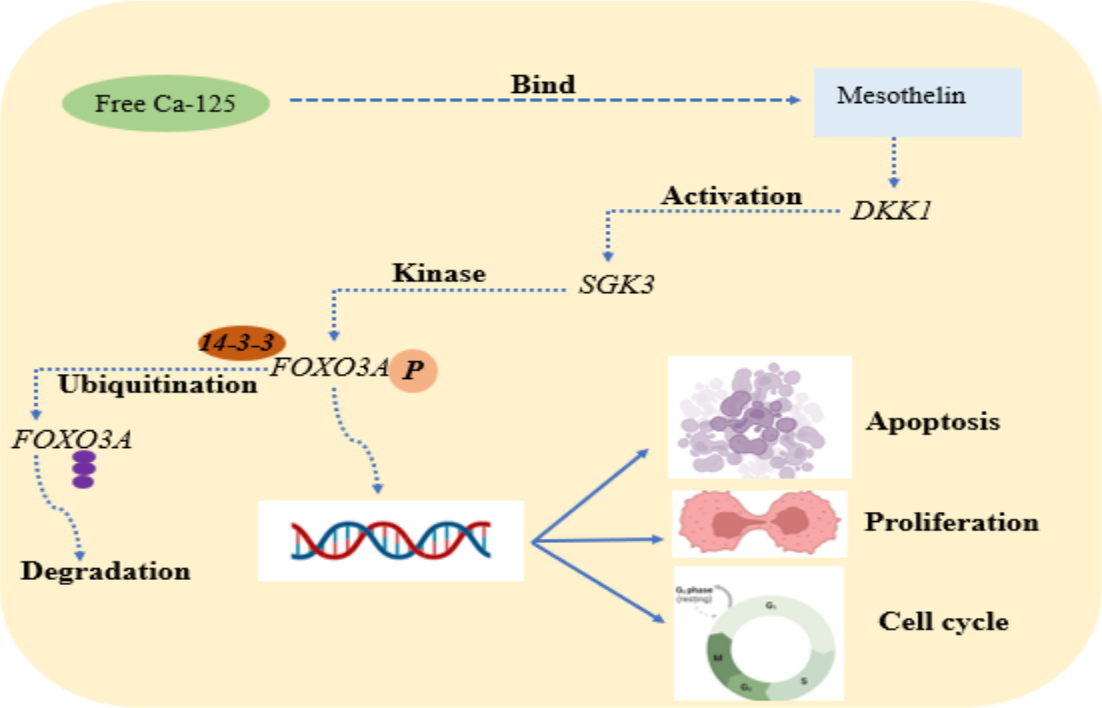

Figure 2. Pathway depicting the interaction between CA125 and mesothelin, facilitating the migration of neoplastic cells and the metastatic spread in advanced serous ovarian carcinoma.
This study evaluates the accuracy of CA-125 in diagnosing and managing ectopic pregnancy (EP), focusing on its association with complications like rupture. Conducted in a large EP patient cohort, it aims to enhance treatment planning and timely interventions, ultimately improving patient care and reducing EP complications.

2. Materials and Methods

The study enrolled 100 patients diagnosed with stable tubal EP who met the inclusion criteria of gestational age under 7 weeks, absence of fetal heart rate (FHR), and lesion size less than 3.5 cm. All participants were eligible for a single-dose methotrexate regimen of 50 units/m² and were recruited from three medical centers (Akbarabadi, Rasul Akram, and Firouzgar) between 2020 and 2022. Patients with a history of ovarian masses, cancer, endometriosis, large uterine fibroids, gastrointestinal inflammatory conditions, or sensitivity to methotrexate were excluded. Serum levels of CA-125 and β-hCG were measured on days 1, 4, and 7 of treatment using the ELISA technique. Throughout the treatment period, patients were monitored for complications such as rupture, hemorrhagic shock, the need for surgical intervention, or a second methotrexate dose. Data were prospectively collected and entered into a database for subsequent analyses. A detailed SPSS file was compiled, encompassing the variables of interest, alongside demographic and laboratory information recorded during hospitalization. Descriptive statistics summarized the data, with quantitative variables reported as means ± standard deviation (SD) and categorical variables as percentages. Statistical analyses were conducted using the latest version of SPSS software, with significance set at $P < 0.05$.

3. Results

The mean age of the study participants was 29.8 ± 6.1 years, ranging from 15 to 41 years. The largest group (34%) consisted of patients in their second pregnancy. The average gestational age was 5.5 ± 0.9 weeks, with a range from 4.1 to 7 weeks. The average initial mass size was 2.1 ± 0.6 cm, with a minimum of 0.8 cm and a maximum of 3.6 cm. Among the participants, 22% (22 patients) required an additional dose of methotrexate, while 30% (30 patients) underwent surgical intervention due to rupture. Single-dose methotrexate treatment was effective in 48% of cases, whereas 52% experienced treatment failure, necessitating either surgery or an additional methotrexate dose.

Statistical analysis demonstrated a significant correlation between elevated CA-125 levels on days 4 and 7 and the requirement for an additional dose of methotrexate, with higher levels observed in these patients ($P < 0.001$) [Table 1]. Furthermore, patients who required surgical intervention due to rupture exhibited significantly higher CA-125 levels on day 1 ($P < 0.001$). Additionally, the average CA-125 levels were significantly greater in patients with treatment failure across all time points ($P < 0.001$) [Table 2].

The relationship between CA-125 and β-hCG levels was evaluated on days 1, 4, and 7, revealing a statistically significant positive correlation at all of the time points ($P = 0.002$, $P = 0.002$, $P < 0.001$, respectively). As β-hCG levels increased, CA-125 levels also demonstrated a corresponding rise ($r = 0.3$, $r = 0.3$, and $r = 0.4$, respectively). However, on day 1, no significant correlation was found between CA-125 and β-hCG in patients with rupture ($P = 0.7$). Further analysis on days 4 and 7 could not be conducted due to limited data (only one patient with rupture had both markers measured). In patients requiring a second dose of methotrexate, no significant correlation was observed on day 1 ($P = 0.06$), but a significant positive correlation was found on days 4 and 7 ($P = 0.002$ and $P = 0.001$, respectively), with higher β-hCG levels being associated with increased CA-125 levels ($r = 0.6$).

The sensitivity and specificity of CA-125 in predicting the need for a second dose of methotrexate were assessed using the ROC curve. On day 1, CA-125 demonstrated an accuracy of 63.6%, with a 95% confidence interval between 0.53 and 0.73. On day 1, a CA-125 level of 28.3 demonstrated 95% sensitivity and 59% specificity, with higher thresholds reducing sensitivity but improving specificity. By day 4, CA-125's predictive accuracy for requiring a second methotrexate dose increased to 91.7% (95% CI: 0.84–0.98), with a threshold of 27.2 yielding 95.5% sensitivity and 89.8% specificity. On day 7, the accuracy remained high at 90.8% (95% CI: 0.83–0.98), with a threshold of 27.2 achieving 95.5% sensitivity and 83.7% specificity. Increasing the threshold consistently improved specificity at the expense of sensitivity.

CA-125 levels were strongly associated with the incidence of rupture and the need for surgery. On day 1, the test showed an accuracy of 97.1% in predicting rupture, with a 95% confidence interval ranging from 0.93 to 1. A CA-125 level of 114 on day 1 exhibited 100% sensitivity and 99.07% specificity for identifying patients at risk of rupture. As CA-125 levels increased, specificity improved, but sensitivity decreased. Due to the lack of CA-125 data for patients who experienced rupture on days 4 and 7 (only one patient had data for these time points), the analysis could not be conducted for those days [Figures 3 and 4].

Table 1. Mean Serum CA-125 Levels on Days 1, 4, and 7 in Patients Requiring a Second Dose of Methotrexate

			CA125 level		
			Day 1	***Day 4***	***Day 7***
the need to take the second dose of MTX	yes	Average	66.1	67	63.8
		Standard deviation	22.4	24.6	27.4
	No	Average	57.5	28.8	29.7
		Standard deviation	47.1	22.7	24.3
	p-value		0.052	<0.001	<0.001

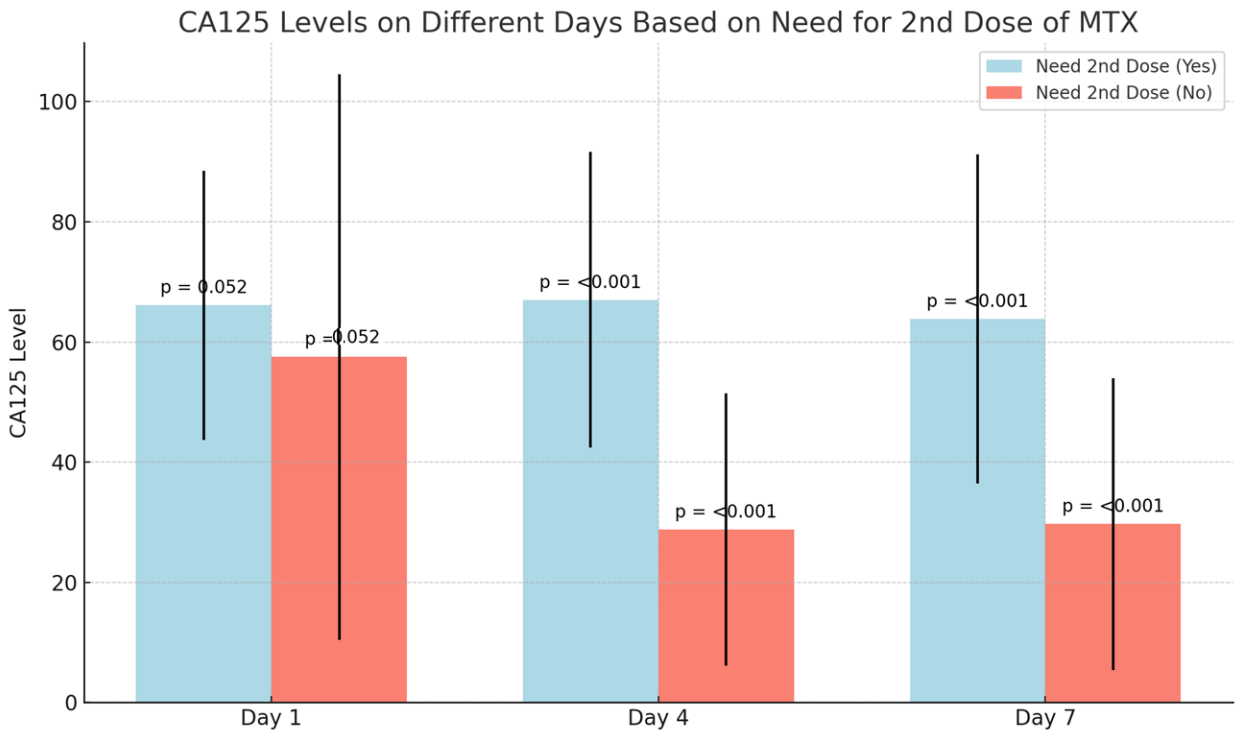

Figure 3. CA-125 level on differnt days based on need for the second dose of methotrexate.

Table 2. Average CA-125 Levels Based on Treatment Outcome

			CA125 level		
			Day 1	***Day 4***	***Day 7***
	Successful	Average	26.5	27	27.9
		Standard deviation	19.2	19.1	20.9
	Failed	Average	89.8	69.1	66.1
		Standard deviation	35.8	26	29
	p-value		<0.001	<0.001	<0.001

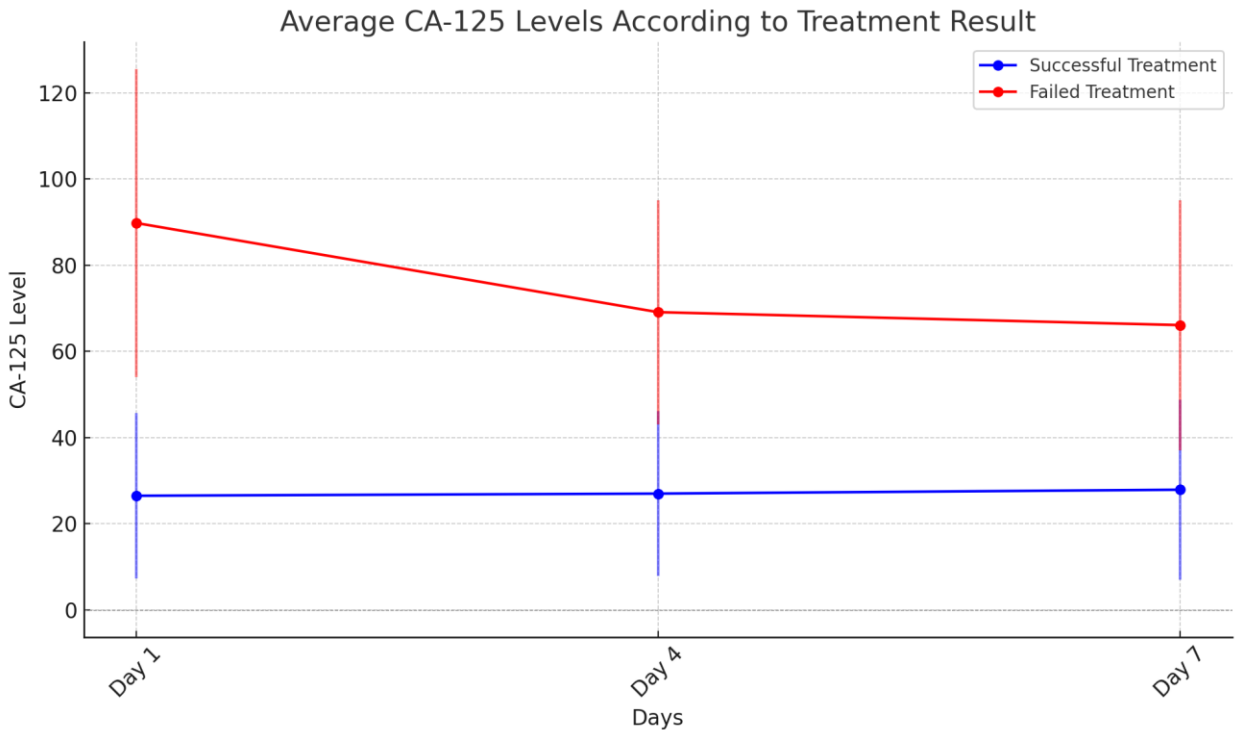

Figure 4. Average CA-125 Levels Based on Treatment Outcome

4. Discussion

Early diagnosis and prompt treatment are crucial for women with EP to prevent complications such as rupture, hemorrhagic shock, and infertility. Timely intervention can significantly improve patient outcomes by reducing the risk of severe morbidity and mortality associated with delayed diagnosis or treatment. Identifying reliable biomarkers, like CA-125, and using them for monitoring can aid in assessing treatment efficacy and predicting the need for further interventions, ultimately enhancing the management of this condition [37]. Previous studies have demonstrated that blood-based biomarkers can play a significant role in identifying ectopic pregnancy (EP), especially in cases where ultrasound fails to accurately determine the location of the fetus. Biomarkers such as human chorionic gonadotropin (hCG) and CA-125 have shown potential in assisting with the diagnosis of EP by providing valuable information about the pregnancy's status and complications. These biomarkers can offer crucial insights when imaging results are inconclusive, thus facilitating earlier and more accurate diagnoses and improving treatment outcomes [38]. Early detection is crucial for effective management. Pregnancy is typically diagnosed through the measurement of β-hCG levels in serum or urine [39]. While β-hCG levels are generally lower in women with ectopic pregnancies than in those with intrauterine pregnancies, a considerable overlap exists between the two groups [40]. A low serum β-hCG level is often associated with a higher likelihood of ectopic pregnancy, while an extremely low level may indicate a more severe clinical condition [41]. Katsikis et al. suggested that assessing both progesterone and CA-125 levels may help differentiate ectopic and incomplete intrauterine pregnancies from normal pregnancies [42,43]. Methotrexate has shown a high success rate as a non-surgical treatment for ectopic pregnancy when used in appropriately selected patients[44]. Higher β-hCG concentrations, on the other hand, may reduce the effectiveness of MTX, often requiring additional doses or surgical management [45]. MTX treatment has been found to reduce serum β-hCG levels, indicating a significant association between elevated β-hCG levels and treatment failure. However, multidose therapy comes with higher costs, increased side effects, and the need for more intensive monitoring, along with continuous

folic acid rescue [46]. This case may be influenced by factors like delayed diagnosis, gestational sac size, and sample size. Typically, a portion of patients requires a second dose of MTX, with a smaller percentage needing more. The study found that CA-125 levels on day 1 were moderately sensitive and accurate in predicting the need for a second MTX dose. Additionally, CA-125 levels were found to correlate with β-hCG in distinguishing fallopian tube abortion from a viable ectopic pregnancy [47].

5. Conclusion

In conclusion, serial measurements of CA-125 in tubal pregnancies can provide valuable insights into the likelihood of gestational sac rupture and the need for either surgical intervention or a second dose of MTX. This study offers evidence supporting the use of CA-125 for the early identification of ectopic pregnancies that require additional intervention, such as a second dose of MTX or surgery. These findings have important clinical implications, as they could help reduce mortality rates in pregnant women and improve future pregnancy outcomes for those with ectopic pregnancies. However, while CA-125 offers valuable insights, its sensitivity and specificity are lower compared to the routine use of β-hCG titers, limiting its effectiveness as a primary diagnostic tool.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Institutional Review Board of Iran University of Medical Sciences (IR.IUMS.FMD.REC.1400.462). Prior to participation, written informed consent was obtained from all patients. All procedures were carried out in compliance with the ethical standards outlined in the Declaration of Helsinki.

Funding

Not applicable

Author's contributions

All authors equally contributed to preparing this article. All authors have read and approved the final manuscript.

Conflict of interest

This paper does not appear to be affected by any competing financial interests or personal relationships of the authors.

Acknowledgments

We would like to extend our appreciation and thanks to all participants, staff, and managers who made this study possible.

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