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RESEARCH ARTICLE

Role of CA-125 as a Predictive Factor for Ovarian Tumors in Iraqi Pregnant Women with Severe Vaginal Bleeding

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Abstract: ***Background***: This case-control study aimed to evaluate the role of Cancer Antigen 125 (CA-125) in Iraqi pregnant women experiencing vaginal bleeding, with a focus on its potential as a diagnostic marker for complications during pregnancy and predictive diagnostic cancer. ***Methods***: A total of 23 pregnant women with vaginal bleeding were enrolled in the study in January 2025. Participants were divided into two groups: 7 women with normal CA-125 levels (control group) and 17 women with elevated CA-125 levels, diagnosed by obstetricians and gynaecologists. Venous blood samples were collected and analysed for CA-125, Vitamin D, and other relevant biochemical markers using standardised laboratory techniques. ***Results***: The mean age of participants was 25.61 ± 3.14 years, with a body mass index (BMI) of 26.83 ± 5.13 kg/m^2. Most women reported bleeding for less than a week (73.91%). Statistical analysis revealed a significant difference in CA-125 levels between the two groups, with the predictive group showing higher levels (67.7 ± 8.77 U/mL) compared to the non-predictive group (20.3 ± 2.54 U/mL; $p < 0.001$). No significant differences were found in Vitamin D levels or other biochemical parameters between the two groups. ***Conclusion***: Elevated CA-125 levels in pregnant women with vaginal bleeding may provide valuable diagnostic insights. Further studies are warranted to explore the clinical implications of CA-125 as a biomarker in obstetric care, particularly in populations with high rates of complications.

Keywords: CA-125, pregnancy, vaginal bleeding, diagnostic marker, Iraq.

INTRODUCTION

Cancer antigen 125 (CA-125), which is an antigenic tumour marker expressed by epithelial ovarian neoplasms and cells lining various organs such as the endometrium, fallopian tubes, pleura, peritoneum, and pericardium[(1&2)] Click or tap here to enter text., is a high-molecular-weight mucinous glycoprotein present on the surface of ovarian cancer cells, has been pivotal in screening, detecting, and managing ovarian cancer for the past 4 decades. However, the rise of CA-125 during normal pregnancy remains unclear. Some previous publications did not find any abnormal rise of CA-125[(3),] While some publications showed high levels of CA-125 in normal pregnancy[(4)] Click or tap here to enter text..

Pregnancy is a crucial period in women's lives where they tend to experience several typical and expected changes in all the maternal organ systems.[(5)],Click or tap here to enter text. Some pregnant women experience health problems during pregnancy, even those who were otherwise healthy before pregnancy. Bleeding complications in pregnant women can occur as a result of an inherited or acquired coagulopathy. Acquired bleeding disorders during pregnancy usually arise acutely during massive postpartum haemorrhage when uterotonics or sutures have failed[(6)]. Click or tap here to enter text.Although pregnancy is associated with alterations in coagulation factors to promote a hypercoagulable state, this is not always sufficient to overcome the bleeding tendency in women with underlying bleeding disorders. Most women will have improvement in their bleeding disorder secondary to these changes; however, they are at risk for significant worsening immediately following delivery[(6)].

Cancer antigen 125 (CA-125), which is an antigenic tumor marker expressed by epithelial ovarian neoplasms and cells lining various organs such as the endometrium, fallopian tubes, pleura, peritoneum, and pericardium[(1,2)]Click or tap here to enter text., a basal serum CA-125 level is due to the secretary function of these organs[(7)]. An increased CA-125 level is due to genital or non-genital origins. Non-genital causes include hepatic diseases, peritonitis, renal failure, breast, colon and lung cancer, and tuberculosis. Genital causes include pelvic inflammatory diseases, endometriosis, adenomyosis, leiomyoma, ectopic pregnancy, endometrial and ovarian cancer. CA-125 increases in pregnancy in the first trimester [(8,9)] .

CA125 also becomes elevated under certain physiological conditions, such as during menstruation, the first trimester of pregnancy, the postpartum period, fibroids, and pelvic endometriosis [(10,11)].

Aim of the study

This study aimed to investigate the role of cancer antigen-125 (CA-125) in Iraqi pregnant women with severe vaginal bleeding, and it can be used as an early diagnostic marker for cancer.

PATIENTS AND METHODS

Subject and Target population: This case-control study was planned to estimate CA-125 in Iraqi pregnant women with vaginal bleeding in Baghdad, Iraq.

In this study, 23 specimens were collected in January 2025 from pregnant women suffering from vaginal bleeding who attended the private clinic in Baghdad province, Iraq.

The specimens were classified into two groups:

- Patients with normal levels of CA-125 (U/ml) (n=7), as the control group, who were without any other systemic disease, and whose ethnic background, age, and sex matched the patient's group.
- Patients with abnormal levels of CA-125 (U/ml) (n=17), as the cancer patients, who were diagnosed clinically by an Obstetrician and gynaecologist, suffering from vaginal bleeding. None of them had any other systemic diseases.

Samples Collection

About 5 mL of venous blood was collected from all participants and dispensed to basic test tubes (Gel tube) then blood has been left to clot and after that, centrifuged at 3000 rpm for 10 min to obtain clear, transparent sera that have been moved to another labeled tube to measure these tests: Vitamin D, GPT, B. Urea, and CA-125.

Methods

Measurement of ALT

ALT in this study was estimated using the Cobas diagnostic kit (Roche/Hitachi Cobas c311), a fully automated clinical chemistry analyser.

This essay follows the recommendations of the IFCC but was optimised for performance and stability.

ALT catalyses the reaction between L-alanine and 2-oxoglutarate. The pyruvate formed is reduced by NADH in a reaction catalysed by lactate dehydrogenase (LDH) to form L-lactate and NAD+.

$$L-Alanine+2-oxoglutarate \xrightarrow{ALT} pyruvate+L-glutamate$$

$$Pyruvate+NADH+H^{+} \xrightarrow{LDH} L-lactate+NAD^{+}$$

The rate of the NADH oxidation is directly proportional to the catalytic ALT activity. It is determined by measuring the decrease in absorbance.

The measuring range of ALT was 5-700 U/L. Determine samples having higher activities via the rerun function. Dilution of samples via the rerun function is a 1:10 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 10.

The **normal range** of ALT is <41 (U/L).

Specimen Collection and Preparation: For serum or Plasma:

1. Following standard phlebotomy procedure, if collecting plasma, use a suitable anticoagulant blood collection tube (Containing heparin sodium, heparin lithium, or sodium citrate).
2. Separate the serum/plasma from the blood as soon as possible to avoid hemolysis.
3. The test should be performed immediately after the specimens have been collected. Do not leave specimens at room temperature for an extended period. Specimens may be kept below -20°C

Statically Analysis

The data were analysed using Microsoft Excel 2023 and IBM SPSS v. 26.0. The results reported in this study were expressed as mean ± Standard Deviation (SD), and frequencies were expressed as percentages (%). For comparisons among distributed groups, ANOVA was performed. Probability values less than 0.05 were considered a biologically significant difference, while those less than 0.01 were regarded as highly significant.

RESULTS

As presented in the

Table (***1*** Below, the mean age of the women in this study was 25.61 ± 3.14 years, and their BMI was 26.83 ± 5.13 kg/m².

Table (1): The descriptive statistics of the sociodemographic variables of the patients

Variables	N	Mean ± SD	Minimum	Maximum
Age (years)	23	25.61±3.14	20	30
BMI (Kg/m²)	23	26.83±5.13	16	37

As presented in the Figure 1**):** Most of the women in this study experienced less than a week of bleeding (73.91%), followed by 17.39% who had greater than a week of bleeding, and only 8.7% had bleeding for a week.

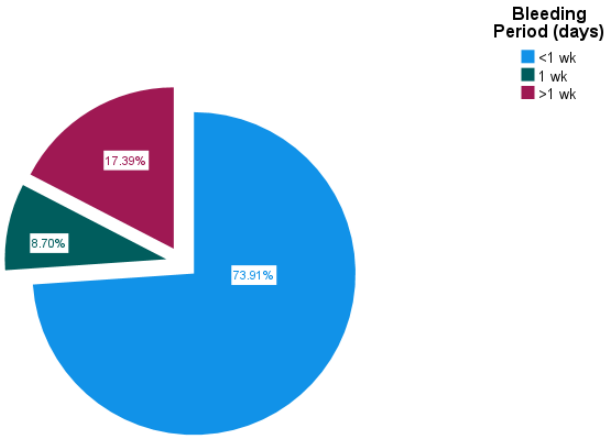


Figure 1): The frequency of the bleeding days of patients in this study

As presented in the Figure 2: Below, most of the women in this study had no abortions (60.87%), while 26.09% of the women had one abortion, and lastly, only 13.04% had two abortions.

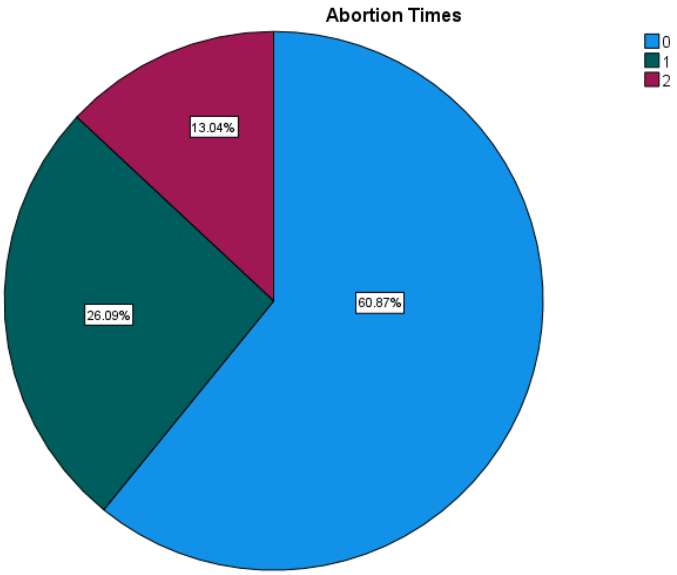


Figure 2: The frequency of the abortion times of patients in this study

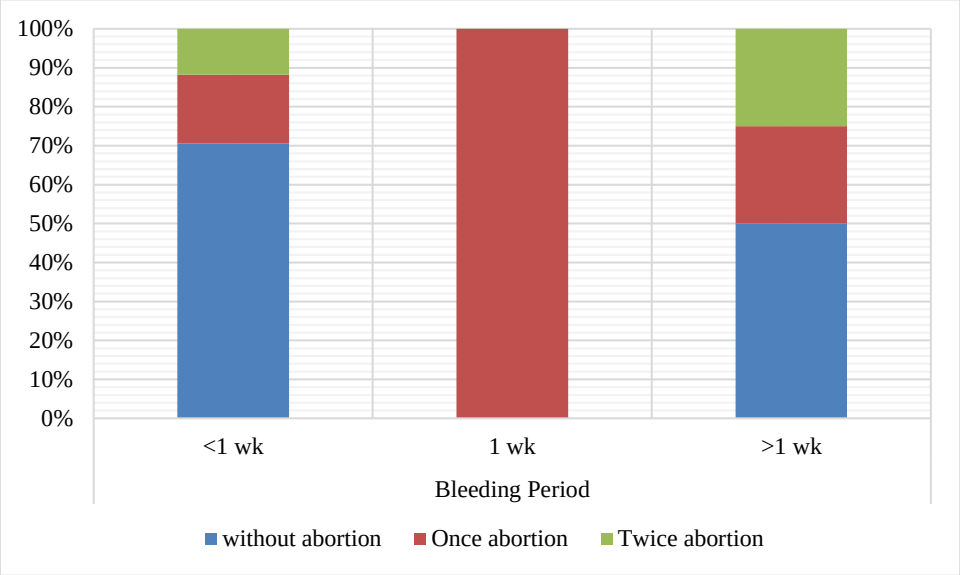
As presented in the

Table(**2):** and Figure(3)**:** Below, most of the women in this study who suffered bleeding for less than a week had not had an abortion (70.6%). In comparison, all of those sustained for a week were with one abortion time (100%), and lastly, most of those suffered for more than a week were without any abortion times (50%).

Table(2): Cross-tabulation between bleeding period and abortion times

		Bleeding Period						Total	
		<1 week		1 week		>1 week			
		N	%	N	%	N	%	N	%
Abortion (times)	0	12	70.60%	0	0.00%	2	50.00%	14	60.90%
	1	3	17.60%	2	100.00%	1	25.00%	6	26.10%

	2	2	11.80%	0	0.00%	1	25.00%	3	13.00%
Total		**17**	**100.00%**	**2**	**100.00%**	**4**	**100.00%**	**23**	**100.00%**



Figure(3): Cross distribution between bleeding period and abortion times

As presented in the

Table(**3):** Below, the predicative group were slightly younger than the non-predicative group (25.5±3.31, 25.86±2.97 years, respectively). The BMI level of the predictive group was 28.63±3.24 kg/m2, which was higher than that of the non-predictive group, which was 22.71±6.47 kg/m2. A highly significant difference was observed between the two groups, with a p-value of 0.008.

The vitamin D level was not significantly different between the two groups, with values of 23.81±9.74 ng/mL in the predictive group and 21±7.75 ng/mL in the non-predictive group. The GPT level was also not significantly different between the two groups, with values of 46.31±12.95 U/L in the predictive group and 54.14±7.13 U/L in the non-predictive group. Additionally, the B. Urea level was not significantly different between the two groups, with values of 49.25±7.95 mg/dL in the predictive group and 46.71±7.23 mg/dL in the non-predictive group.

There was no significant difference in bleeding period between the two groups; it was 4.13±2.9 days in the predictive group and 3.57±2.37 days in the non-predictive group. Also, the abortion times were not significantly different between the two groups; it was 0.5±0.73 times in the predictive group and 0.57±0.79 times in the non-predictive group. The CA-125 level was significantly different between the two groups; it increased to (67.7±8.77 U/mL) in the predictive group compared to the non-predictive group, which was (20.3±2.54 U/mL).

Table(3): The statistical analysis of the study variables

Variables	Groups	N	Mean ± SD	Min	Max	F	Sig.
Age (years)	Non-predicative	7	25.86 ± 2.97	22	30	0.060	0.809
	Predicative	16	25.5 ± 3.31	20	30		
	Total	23	25.61 ± 3.14	20	30		
BMI (Kg/m^2)	Non-predicative	7	22.71 ± 6.47	16	34	8.731	**0.008**
	Predicative	16	28.63 ± 3.24	24	37		
	Total	23	26.83 ± 5.13	16	37		
Vitamin D (ng/mL)	Non-predicative	7	21 ± 7.75	11	29	0.454	0.508
	Predicative	16	23.81 ± 9.74	11	41		
	Total	23	22.96 ± 9.1	11	41		
GPT (U/L)	Non-predicative	7	54.14 ± 7.13	46	67	2.225	0.151
	Predicative	16	46.31 ± 12.95	13	65		
	Total	23	48.7 ± 11.9	13	67		
B. Urea (mg/dl)	Non-predicative	7	46.71 ± 7.23	35	56	0	. 0

	Predicative	16	49.25 ± 7.95	36	64		
	Total	23	48.48 ± 7.67	35	64		
Bleeding Period (days)	Non-predicative	7	3.57 ± 2.37	1	8	0.197	0.662
	Predicative	16	4.13 ± 2.9	1	10		
	Total	23	3.96 ± 2.71	1	10		
Abortion Times	Non-predicative	7	0.57 ± 0.79	0	2	0.045	0.835
	Predicative	16	0.5 ± 0.73	0	2		
	Total	23	0.52 ± 0.73	0	2		
CA-125 (U/mL)	Non-predicative	7	20.3 ± 2.54	16.78	25.08	192.561	**0.000**
	Predicative	16	67.7 ± 8.77	50.54	80.92		
	Total	23	53.27 ± 23.48	16.78	80.92		

Note: depending on the cut-off value, if it is greater than 36 U/mL, the CA-125 will be predictive.
The results in the Table**(4):** The results below indicate that there was not a significantly low negative correlation between age and CA-125, with a Pearson correlation of (-0.015) and a P-value of (0.494). The results revealed that there was a moderate correlation between BMI and CA-125, with a Pearson correlation of (-0.15) and a P-value of (0.05).

Table(4): The correlation between the age, BMI, and CA-125

Variables		Age	BMI	CA-125
Age	r	1	0.074	-0.15
	P		0.736	0.494
BMI	r	0.074	1	0.411
	P	0.736		0.051
	P	0.634	0.476	0.794
CA-125	r	-0.15	0.411	1
	P	0.494	0.051	

The results in Table(4): Indicate that there was not a significantly low correlation between Vit D and CA-125, with a Pearson correlation of 0.189 and a P-value of 0.387. While there was not a significantly low negative correlation between GPT and CA-125, with a Pearson correlation of (-0.262) and a P-value of (0.226). Lastly, there was no correlation between B. urea and CA-125, with a Pearson correlation of 0.005, and it was not significant with a P-value of 0.98.

Table(4): The correlation between the Vit D, GPT, B. Urea, and CA-125 variables

Variables		Vit D	GPT	B. Urea	CA-125
Vit D	r	1	-0.066	0.069	0.189
	P		0.765	0.755	0.387
GPT	r	-0.066	1	-0.132	-0.262
	P	0.765		0.549	0.226
B. Urea	r	0.069	-0.132	1	0.005
	P	0.755	0.549		0.98
CA-125	r	0.189	-0.262	0.005	1
	P	0.387	0.226	0.98	

The results in the Table**(6)** The results below indicate that there was no significant correlation between bleeding days and CA-125, with a Pearson correlation of 0.017 and a P-value of 0.938. The results revealed that there was a low correlation between abortion times and CA-125, with a Pearson correlation of 0.219 and a P-value of 0.315.

Table(6): The correlation between the bleeding days, abortion times, and CA-125

Variables		Bleeding days	Abortion Times	CA-125
Bleeding (days)	r	1	0.219	0.017
	P		0.315	0.938
Abortion Times	r	0.219	1	-0.058
	P	0.315		0.794
CA-125	r	0.017	-0.058	1
	P	0.938	0.794	

DISCUSSION

In this study, the mean age of the women was 25.61±3.14 years, and the BMI was 26.83±5.13 Kg/m^2. Most of the women in this study who suffered bleeding for less than week were without any abortion times (70.6%), while all of those suffered for a week were with once abortion time (100%), and lastly, most of those suffered for a greater than a week were without any abortion times (50%). We found that CA-125 was significantly increased in pregnancies with vaginal bleeding. According to this study, the CA-125 may be used as a diagnostic marker in these pregnancies.

Various physiological and pathological conditions, such as renal failure, pancreatic and hepatobiliary disease, lung disease, systemic disease, inflammation, menstruation, and pregnancy, can induce significant variations in plasma concentrations of tumor markers[(12)]. These markers have previously been investigated in the biological fluids of healthy pregnant and non-pregnant women. The presence of considerable concentrations of tumor markers during pregnancy may be attributed to their involvement in biological functions associated with fetal development, differentiation, and maturation[(13)]. One of these tumor markers, CA-125 is mostly used as a serum marker for malignancies. In a prospective longitudinal study, serum concentrations of CA 125, CA 15-3, CA 19-9, and CEA were followed in healthy pregnant women throughout pregnancy[(14)].

In this study, the predicative group were slightly younger than the non-predicative group (25.5±3.31, 25.86±2.97 years, respectively). The BMI level of the predictive group was 28.63±3.24 kg/m2, which was higher than that of the non-predictive group, which was 22.71±6.47 kg/m2. A highly significant difference was observed between the two groups, with a p-value of 0.008. The vitamin D level was not significantly different between the two groups, with values of 23.81±9.74 ng/mL in the predictive group and 21±7.75 ng/mL in the non-predictive group. The GPT level also was not significantly different between the two groups; it was 46.31±12.95 U/L in the predictive group and 54.14±7.13 U/L in the non-predictive group. Also, the B. Urea level was not significantly different between the two groups; it was 49.25±7.95 mg/dl in the predictive group and 46.71±7.23 mg/dl in the non-predictive group. There was no significant difference in bleeding period between the two groups; it was 4.13±2.9 days in the predictive group and 3.57±2.37 days in the non-predictive group. Also, the abortion times were not significantly different between the two groups; it was 0.5±0.73 times in the predictive group and 0.57±0.79 times in the non-predictive group. The CA-125 level was significantly different between the two groups; it increased to (67.7±8.77 U/mL) in the predictive group compared to the non-predictive group, which was (20.3±2.54 U/mL). A significant increase in serum CA-125 levels was also reported in a group of patients with vaginal bleeding and impending spontaneous abortion[(15,16)], as presented in this study. It was concluded that the extension of decidual destruction and trophoblast separation from decidual cells was the primary source of the maternal serum CA-125 elevation; however, this has not been supported by other studies [(17,18)]. A connection between serum CA-125 levels and abnormal early intrauterine pregnancies has been investigated to determine whether it might be helpful in the assessment of threatened abortion or not. It was believed that the destruction of fetal tissues and decidua would yield different serum CA-125 values in patients with threatened abortion compared with those with normal intrauterine pregnancies. One of the cross-sectional studies has reported significantly lowered serum CA-125 concentrations in women with ectopic pregnancies[(17)]. The low CA-125 levels were explained by the impaired interaction between the fetal trophoblast and tubal mucosa[(15)].

Kobayashi *et al.*, (1989) stated that the serum CA-125 levels are high in women with normal early pregnancy, spontaneous abortion, and hydatidiform mole. Still, the same levels are low in women with tubal pregnancy, especially if there had been no uterine bleeding[(18)]. They reported that a transient elevation of the CA-125 level occurred in maternal serum during early pregnancy and just after delivery, and they thought that the destruction of decidual tissues may cause this transient elevation of CA-125[(19)]. Another study found elevated serum CA-125 levels in a majority of women with normal intrauterine

pregnancies[20]. They found lower levels of CA125 in the women with abnormal pregnancies, in which there should be an increased incidence of bleeding. Correction of this clinical finding would potentially increase the differences noted between normal and abnormal pregnancies. Moreover, they reported that as significant differences exist in the maternal serum CA125 levels between early, normal, and ectopic gestations, CA-125 may prove to be clinically helpful in early pregnancy monitoring.

CA-125 is the most reliable serum marker, but its role in screening is controversial[19]. In the study by[20], the authors examined the usefulness of CA-125 with a cut-off of 35 U/ml; the sensitivity, specificity, PPV, and NPV were 78.9%, 86.9%, 63.8%, and 93.3%, respectively. CA-125 with a cutoff of 35 U/ml was detected in 30 of the 38 malignant cases. CA-125 with a cut-off of 35 U/ml, LR+ = 6.03, and LR- = 0.24 were detected, namely, high CA-125 gave one false positive result for each six positive results. According to these values, the diagnostic odds ratio was found to be 25 for CA-125 with a cutoff of 35 U/ml. The sensitivity and specificity of CA-125 for ovarian carcinoma varied between 56% and 100% and 60% and 92%, respectively, for differentiation in the diagnosis of adnexal masses according to the selected cut-off values[21].

In the study by[22], four out of 38 cases were mucinous type ovarian carcinoma, and CA19-9 was elevated in two patients. In both of these cases, due to high CA-125, CA19-9 could not provide an additional contribution to the pre-diagnosis. In the study performed by Fioretti et al., in women diagnosed with ovarian mass with an age of 50 years or more, according to the use of CA-125 alone for differentiation of benign and malignant masses, higher sensitivity (93.2% vs. 81.1%, $p = 0.03$, $p < 0.05$) and non-significant specificity (78.9% vs. 86%, $p < 0.05$) were detected for the combination of CA-125 (cut-off 65 U/ml) and CA19-9, respectively[23] .

Tayyar and Tutus reported that maternal serum and amniotic fluid CA 19-9 levels were elevated in primigravidas and in pregnant women with female fetuses[24],There have been several reports that CA 125 might be used as a diagnostic marker in some pathological pregnancies. To the best of our knowledge, the present study on the relationship between CA 125 and vaginal bleeding is the first such report in the literature. One survey by[25] showed that the serum CA-125 level is higher in normal pregnancy compared to ectopic pregnancy (EP) 2-4 weeks after missed menses. In contrast, another study (17) found a higher CA-125 level in EP compared with normal pregnancies.

In our study, a low correlation was observed between bleeding days and CA-125, with a Pearson correlation coefficient of 0.017, which was not statistically significant, as indicated by a P-value of 0.938. The results revealed that there was a low correlation between abortion times and CA-125, with a Pearson correlation of 0.219 and a P-value of 0.315. The study by[26] reported that the median CA-125 level in the normal pregnancy was less than that in the threatened abortion group that aborted with the same gestational weeks ($P < 0.001$). Moreover, the median values and dispersion ratios of CA-125 levels in the REP group showed similarity to those in the NIUP group ($P > 0.05$). They think that such a situation can be explained by the disruption of decidual tissue, resulting from an inevitable abortion. The results of our study are in line with those of several studies regarding the high levels of CA-125 in early intrauterine pregnancy (18,27). Nevertheless, our findings, concerning the CA-125 levels in ectopic pregnancy, have shown a partial contradiction or resemblance with the findings of published studies. According to these findings, it can be stated that the test is rather sensitive to differentiating between a normal pregnancy and a threatened abortion. There was no significant correlation between CA-125 levels and gestational weeks in the two groups. Therefore, an increase in serial CA 125 measurements in the follow-up of pregnancies with vaginal bleeding could be an early signal in determining the progression to pregnancy loss. Fiegler et al. (2003) revealed that all the women with symptoms of imminent abortion who have a CA-125 level of > or = 43 IU/ml should be considered at a greater risk of miscarriage[28].
The findings of this study indicated that there was no significant correlation between vitamin D and CA-125, with a Pearson correlation of 0.189 and a P-value of 0.387. While there was not a significantly low negative correlation between GPT and CA-125, with a Pearson correlation of (-0.262) and a P-value of (0.226). Lastly, there was no correlation between B. urea and CA-125, with a Pearson correlation coefficient of 0.005, which was not significant with a P-value of 0.98. Vitamin D is required to maintain proper levels of calcium and phosphorus, so inadequate Vitamin D in pregnancy may lead to abnormal bone growth, fractures or rickets in newborns. Deficiency of Vitamin D has been linked with higher risk of pregnancy complications such as pre-eclampsia, preterm birth, low birth weight and gestational diabetes[29]. Our study revealed that hypovitaminosis D in pregnant women is prevalent, and the contributing factors might be low dietary intake and lack of sunshine. Another explanation could lie in the prolonged deficiency of dietary calcium intake because of the eating habits in Iraq. Vitamin D deficiency is observed worldwide in all age groups[30].

CONCLUSION

- The study found significantly elevated CA-125 levels in Iraqi pregnant women with vaginal bleeding, indicating its potential role as a diagnostic marker.
- Most participants experienced vaginal bleeding for less than a week, with a notable correlation to previous abortion history.
- The mean Body Mass Index (BMI) was higher in the predictive group, suggesting a potential

link between obesity and abnormal CA-125 levels.

- Vitamin D deficiency was prevalent among the participants, highlighting a public health concern that may affect pregnancy outcomes.

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