

The role of D-dimer with beta-human chorionic gonadotropin, progesterone and cancer antigen-125 as markers for miscarriage

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Received: 1 May 2021

Revised: 28 May 2021

Accepted: 30 May 2021

Published: xx xx 2020

Journal of The Arab Society for Medical Research 2021, 16:84–90

Background/Aim

Miscarriage is defined as pregnancy termination before the 20th week of gestation or if a baby's birth weight is more than 500g. Approximately 10–12% of all gestations worldwide end with a miscarriage. We aimed in this study to evaluate the role of serum level of D-dimer along with beta-human chorionic gonadotropin (β -HCG), progesterone, and cancer antigen-125 (CA-125) in the prediction of first trimester miscarriage.

Patients and methods

A total of 400 pregnant women from the Centre of Excellency Clinic, National Research Centre, Egypt, were recruited in this study at the fifth week of gestational age. Patients were divided into two groups: group 1 included patients whose pregnancy was completed ($n=356$), and group 2 included patients who had miscarriage ($n=44$). Serum level of D-dimer was measured by enzyme-linked fluorescence assay, whereas serum levels of β -HCG, progesterone, and CA-125 were measured by using an enzyme-linked immunosorbent assay technique at the fifth week and 13th week of gestation for all participants, and then they underwent follow-up until 20 weeks of pregnancy.

Results

Pregnancy was completed in 356 women (group 1), whereas miscarriage occurred in 44 women (group 2). At the fifth week and 13th week of gestation, the serum level of D-dimer in the fifth week was insignificant, but it became significant in the 13th week. β -HCG and progesterone were found significantly lower, whereas the level of CA-125 was found higher in women who aborted (group 2).

Conclusion

During the first trimester, maternal serum markers such as D-dimer with β -HCG, progesterone, and CA-125 levels represent early, noninvasive techniques to predict miscarriage.

Keywords:

cancer antigen-125, D-dimer, miscarriage, progesterone, beta-human chorionic gonadotropin

J Arab Soc Med Res 16:84–90

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1687-4293

Introduction

According to the WHO, the Centers for Disease Control and Prevention, and the National Center for Health Statistics, miscarriage is defined as pregnancy termination before the 20th week of gestation or if a baby's birth weight is less than 500 g [1].

One of the most confirmative tools for diagnosing early pregnancy failure is ultrasound scanning, which represents the single most available superlative diagnostic and prognostic technique. Nevertheless, in certain particular conditions, both clinical (vaginal bleeding) and ultrasonographic findings are nonspecific in predicting the pathway of pregnancy. Consequently, confirming the viability of pregnancy necessitates highly specific and sensitive biomarkers, which is essential for early intervention [2].

D-dimer is a small protein portion found in the blood after the fibrinolysis process (degradation/breakdown of a thrombus). The name 'D-Dimer' is derived from the fact that it contains two D fragments cross-linked by a fibrin protein. The determination of D-dimer helps in the diagnose of thrombosis. As studies have shown a strong correlation between abortion and the prethrombotic state, hence screening abortion can be done by strengthening the testing of the prethrombotic state [3].

However, assessment of D-dimer as a significant hematological index can reflect the important

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changes in both thrombosis and fibrinolysis dynamic processes [4]. The increased fibrin turnover is regarded as the consequence of elevated procoagulation activity, which is indicated by higher concentrations of D-dimers. Therefore, D-dimers are regarded as the most sensitive markers of secondary fibrinolytic activation, with successive trimester [5]. Recent studies have concluded that fibrinolysis and abnormal coagulation/thrombosis could lead to severe maternofetal morbidity and mortality. Moreover, elevated blood levels of D-dimer are associated with many pregnancy complications, that is, hypertension during pregnancy, placental abruption, repeated abortion, preterm birth, postpartum hemorrhage, and disseminated intravascular coagulation [6].

Inside the placenta, syncytiotrophoblast released a glycoprotein known as human chorionic gonadotropin (HCG), which is made with A and B units. The highest level of HCG occurs during the 10th gestational week, and it continues to be secreted throughout the length of pregnancy [7]. All through a process of implantation, HCG represents the first hormonal signal of conception. However, maternal hormonal factors together with other fetoplacental factors probably play a potential role in regulating the apoptotic signaling molecules [8]. For the progression of pregnancy, beta-human chorionic gonadotropin (β -HCG) is essential in supporting and conserving the function of the corpus luteum (CL) [9].

Progesterone, the C-21 steroid hormone released from granulosa cells inside the ovary, stimulates the endometrial decidualization for blastocyst implantation, in addition to maintaining pregnancy [2]. The CL in the ovary releases progesterone, which is the cornerstone for the continuity of pregnancy until the sixth to seventh week of gestation. Until about the 10th gestational week, progesterone is mainly produced by the CL. After the 10th gestational week, the placenta exclusively takes over the process of progesterone secretion. Moreover, the half-life time of progesterone in the blood is less than 1 h; consequently, factors affecting trophoblasts' viability will result in a rapid decrease in progesterone level [5]. However, several studies have reported progesterone level as the most specific biomarker for distinguishing viable from nonviable pregnancies [2].

Cancer antigen-125 (CA-125) can be defined as a cell-surface antigen with high molecular weight. In about 80% of nonmucus epithelial carcinomas of the ovary,

CA-125 can be detected as a mucin-like coelomic antigen. This antigen can be detected in the secretion from normal tissues (e.g. amnion and coelomic epithelium) and their derivatives such as mesenteric organs, respiratory system, and epithelial tissue of the female genital system. It has been reported that an increased level of CA-125 is owing to genital or nongenital origins. Peritonitis, endometriosis, adenomyosis, renal failure, leiomyoma, hepatic diseases, ectopic pregnancy, and breast, colon, lung, endometrial, and ovarian cancers are all considered as nongenital etiological factors [10]. Although some previous studies have found an increased incidence of miscarriage in cases of elevated levels of CA-125, yet other studies have found no statistically significant difference in the levels of CA-125 when comparing the ongoing pregnancy cases with those with miscarriage. Moreover, the risk of miscarriage in patients with higher levels of CA-125 was not elevated [11].

Implantation derived by an extreme molecule is faced with the complexities and difficulties of such molecule, and consequently, this leads to rejected pregnancies ending in miscarriage (17% failure rate) and biochemical pregnancies (25% failure rate). Several authors have studied the prognostic value of β -HCG in threatened miscarriage [12].

Patients and methods

Patients

This study was conducted from January 2018 to December 2019 on 400 pregnant women who attended the outpatient clinic of obstetrics and gynecology at Centre of Excellency Clinic, National Research Centre, Egypt, at the fifth and 13th week of gestational age and underwent follow-up until 20 weeks of pregnancy, as miscarriage is defined as pregnancy termination before 20 weeks of gestation. Inclusion criteria included maternal age between 20 and 40 years; BMI 20–30 kg/m²; singleton pregnancy; and visible gestational sac of a living embryo, verified by visualized cardiac activity on real-time ultrasound.

Pregnant women were excluded if they had any of the following: a potential source of elevated D-dimer: family or personal history of venous thromboembolic disease; advanced maternal age (>45 years); morbid obesity (BMI > 40 kg/m²); family or personal history of antiphospholipid syndrome; suspected or confirmed deep vein thrombosis; history of smoking; multiple gestations; current infection and fever; coagulation disorders; women who received anticoagulation prophylaxis; history of any general medical disease,

for example, diabetes or thyroid disease; history of any maternal disease that would cause an increase in CA-125 levels such as chronic pelvic infection and endometriosis; or presence of local gynecological disease or malformation, for example, fibroid, adnexal masses, hypoplastic uterus, or septate uterus (excluded by normal appearance of the uterus and ovaries by ultrasound).

Ethical approval

This is a cross-sectional study. It was approved by the Medical Research Ethics committee of the National Research Centre, Cairo, Egypt, under registration number 18–149. All participants were informed about this study, and written consent was taken from each of them.

Study design

The study was carried out on 400 pregnant women, and they were divided after following them up until 20 weeks into two groups:

Group 1: women whose pregnancy was completed ($n=356$).

Group 2: women whose pregnancy was terminated by miscarriage ($n=44$).

The gestational age was calculated from the first day of the last menstrual period. For all participants, serum levels of D-dimer, β -HCG, progesterone, and CA-125 were measured at the fifth week and 13th week of gestation. All women were followed up in the form of routine antenatal care, and data were collected when 20 weeks of gestation were reached.

Methods

All participants were subjected to full history taking and complete general and gynecological examination. BMI (kg/m^2) was measured by calculating women's weight in kilogram (kg) and their height in meter square (m^2) [13].

Ultrasound studies

Preliminary ultrasound examination was done with the same experienced operator to calculate gestational age and assess fetal viability as well as to exclude any uterine malformations. Ultrasound scanning was performed on all patients using Medison x8 (Seoul, South Korea), scanner with 4–7-MHz endovaginal probe. Ultrasound parameters also included gestational sac diameter, fetal crown-rump length (diameter), fetal heart rate, and the presence/absence of subchorionic hematoma (collection between the uterine wall and the chorionic membrane).

Blood sampling and markers assay

Venous blood samples (10 ml) were collected from all participants and divided into two portions. The first portion (about 2 ml) was put in a heparinized tube to determine D-dimer, whereas the remaining 7 ml was put into plain tubes, allowed to clot, and the sera were separated after centrifugation at 3000 rpm for 10 min. D-dimer was determined in plasma by enzyme-linked fluorescence assay [D-Dimer Exclusion II (DEX2) kit [14], using VIDAS analyzer (bioMerieux, Seoul, South Korea)]. β -HCG [15], progesterone [16], and CA-125 [17] were measured using an enzyme-linked immunosorbent assay technique, following the instructions on the kit.

Sample size

To compare women who completed their pregnancy with women who aborted, a sample size calculation was done using Stats Direct statistical software, version 2.8 for MS Windows (Stats Direct Ltd, Cheshire, UK). We calculated a minimum proper sample size to be 35 patients for each group to be able to reject the null hypothesis with 80% power ($\beta=0.2$) and 95% significance level ($\alpha=0.05$). The study was carried out on 400 pregnant women.

Statistical analysis

Statistical analyses were performed using the SPSS (version 25; SPSS Inc., Chicago, Illinois, USA). The distribution of the measured variables was determined using the Shapiro test. Normally distributed variables are presented as means $\pm$ SD. Statistical significance of differences for normal distributed numerical data was tested using the Student t test. Categorical data differences were compared by the χ^2 test. Receiver operating characteristic (ROC curve) analysis was used to determine the best cut-off value with its sensitivity and specificity. For all statistical tests, the P value was considered statistically significant if less than 0.05.

Results

The study was carried out on 400 pregnant women. Pregnancy was completed in 356 women (group 1; 89%), whereas miscarriage occurred in 44 women (group 2; 11%). Among the 44 aborted women, only eight women aborted before 13 weeks of gestation. Table 1 compares the demographic characteristics of women of both groups. Both groups showed no significant differences in age or BMI (P values were 0.861 and 0.398, respectively).

Table 2 compares the hormonal profile of women of both groups during the fifth week of gestation. Women

Table 1 Demographic data of women of both groups

	Group 1 (N=356)	Group 2 (N=44)	P value
Age (year)	25.11±2.76	25.03±2.87	0.861 (NS)
BMI	26.12±2.89	26.47±2.55	0.398 (NS)

All data are represented as mean±SD. Statistically insignificant at P value more than 0.05, using unpaired *t* test.

Table 2 Hormonal profile of women of both groups during the fifth week of gestation

	Group 1 (N=356)	Group 2 (N=44)	P value
D-dimer (ng/ml) at 5th week	267.37 ±108.3	301.23 ±135.82	0.112 (NS)
β-HCG (IU/ml) at 5th week	201.56 ±61.13	129.21 ±59.87	<0.001*
Progesterone (ng/ml) at 5th week	34.11±9.39	18.95±5.52	<0.001*
CA-125 (U/ml) at 5th week	25.81±4.59	31.68±4.81	<0.001*

All data are represented as mean±SD. β-HCG, beta-human chorionic gonadotropin; CA-125, cancer antigen-125. Statistically insignificant at P value more than 0.05, using unpaired *t* test.

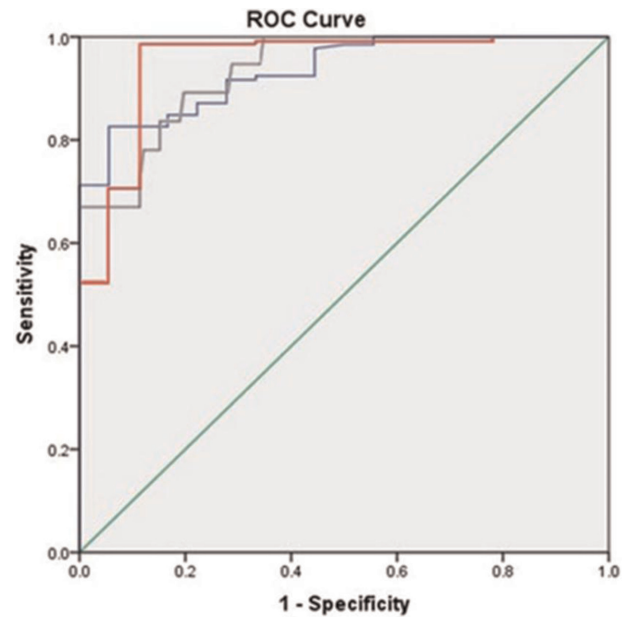
*Statistically significant at P value less than 0.05, using unpaired *t* test.

who aborted (group 2) had a significantly lower level of serum β-HCG and progesterone ($P<0.001$) and a significantly higher level of CA-125 ($P<0.001$) than women of group 1. However, there is no significant difference between both groups regarding D-dimer. ROC curve in Fig. 1 revealed that the cutoff values of β-HCG, progesterone, and CA-125 at fifth week to predict miscarriage were 141.19 IU/ml, 23.1 ng/ml, and 29.8 U/ml, respectively, with a sensitivity of 82.7, 99.2, and 89.5%, respectively; specificity of 94.7, 88.6, and 81.2%, respectively; and area under the curve of 0.934, 0.950, and 0.933, respectively.

Table 3 compares the hormonal profile of women of both groups during the 13th week of gestation. Women who aborted (group 2) also had a significantly lower level of serum β-HCG and progesterone ($P<0.001$) and a significantly higher level of D-dimer and CA-125 ($P<0.001$) than women of group 1. ROC curve in Fig. 2 revealed that the cutoff values of D-dimer, β-HCG, progesterone, and CA-125 at 13th week to predict miscarriage were 635.8 ng/ml, 162.74 IU/ml, 26.88 ng/ml, and 28.1 U/ml, respectively, with a sensitivity of 77.5, 72.5, 98.5, and 89.4%, respectively; specificity of 87.9, 84, 89.1, and 89.5%, respectively; and area under the curve 0.891, 0.843, 0.975, and 0.946, respectively.

Discussion

Spontaneous abortion or pregnancy loss represents a public medical problem in reproductive-age women. It

Figure 1

ROC curve of β-HCG (blue), progesterone (red), and CA-125 (gray) at fifth week, where sensitivity was 82.7, 99.2, and 89.5%, respectively, and specificity was 94.7, 88.6, and 81.2%, respectively. β-HCG, beta-human chorionic gonadotropin; CA-125, cancer antigen-125; ROC, receiver operating characteristic.

Table 3 Hormonal profile of women of both groups during the 13th week of gestation

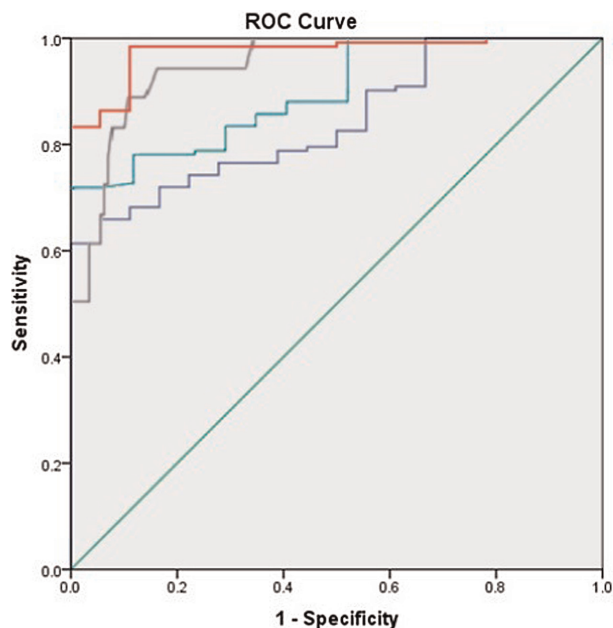
	Group 1 (N=356)	Group 2 (N=36)	P value
D-dimer (ng/ml) at 13th week	420±63.8	950±49.8	<0.001*
β-HCG (IU/ml) at 13th week	214.94 ±68.73	139.83 ±52.79	<0.001*
Progesterone (ng/ml) at 13th week	34.62±10.82	23.86±7.03	<0.001*
CA-125 (U/ml) at 13th week	24.66±5.62	32.37±8.07	<0.001*

All data are represented as mean±SD. β-HCG, beta-human chorionic gonadotropin; CA-125, cancer antigen-125. *Statistically significant at P value less than 0.05, using unpaired *t* test.

represents about 25% of all pregnancy cases. Medically, abortion is defined as pregnancy losses before 20th week of gestation. Abortion/miscarriage results in significant psychological and emotional distress to both the patient and the attendant physician. However, parameters of thrombosis, coagulation, and fibrinolysis are clearly and distinctly disturbed in pregnant women having different complicated health problem [18].

This work was done at the National Research Centre, the Center of Excellency Clinic, aiming to detect predictive biochemical tools for first-trimester abortion from women attending antenatal care. Serum levels of β-HCG, progesterone, CA-125, and

Figure 2



ROC curve of D-dimer (green), β -HCG (blue), progesterone (red), and CA-125 (gray) at the 13th week, where sensitivity was 77.5, 72.5, 98.5, and 89.4%, respectively, and specificity was 87.9, 84, 89.1, and 89.5%, respectively. β -HCG, beta-human chorionic gonadotropin; CA-125, cancer antigen-125; ROC, receiver operating characteristic.

D-dimer were assessed at the fifth week and 13th week of gestation. Women were classified into two groups: the one that completed their pregnancy and another group that aborted.

Our study concluded that pregnancy was completed in 356 women (group 1), whereas miscarriage occurred in 44 women (group 2). At the fifth week and 13th week of gestation, the levels of serum β -HCG and progesterone were found to be significantly lower between the two groups, whereas the level of CA-125 was found higher in women who aborted, having sensitivity of 82.7, 99.2, and 89.5%, respectively, and specificity of 94.7, 88.6, and 81.2%, respectively, at the fifth week. However, at the 13th week, it was found that the sensitivity was 72.5, 98.5, and 89.4% respectively, and specificity was 84, 89.1, and 89.5%, respectively. The serum level of D-dimer was statistically insignificant in the fifth week but was significant at the 13th week, with a sensitivity of 77.5% and specificity of 87.0% for 635.8 ng/ml as a cutoff value.

Many studies have evaluated the role of β -HCG, progesterone, and CA-125, either alone or combined, in the prediction of miscarriages. In agreement with such previous studies, our findings revealed that the β -HCG levels in the group with miscarriage were significantly lower than those of the group who completed their

pregnancy. Regarding the fact that β -HCG is secreted from trophoblasts, it becomes easier to explain the low levels of β -HCG among various cases of miscarriage as inevitable, complete, and incomplete miscarriage.

Eid and Abdallah [19] have reported that both progesterone and CA-125 have excellent specificity and good sensitivity, and hence they are regarded as good predictors for the outcome of first trimester of pregnancy in both normal women and those with threatened abortion. They have concluded that the sensitivity, specificity, positive predictive value, and negative predictive value of CA-125 and progesterone in predicting the occurrence of abortion were 80.66, 100, 100, and 95.4%, respectively, and 78.88, 97.05, 93.7, and 01.3%, respectively.

Hanita and Hanisah [2] conducted a study in which they enrolled 95 pregnant women of 13 weeks or less period of amenorrhea, in addition to 14 normal pregnant women as a control group. They concluded that progesterone levels were significantly declined in cases with a threatened miscarriage that ended up with nonviable fetuses. This result was in agreement with ours throughout the first trimester.

On the contrary, Darwish *et al.* [20] used biochemical markers in their prospective controlled study of pregnant women with recurrent miscarriage between the sixth and 11th week of gestation. They concluded that progesterone is insignificant for the prediction of pregnancy outcome between sixth and seventh gestational weeks. In addition, progesterone sensitivity and specificity were found to be 43 and 50%, respectively, and with a positive predictive value and a negative predictive value of 38 and 56%, respectively. This disagreement may be related to their small sample size.

Similar to our results, Duan *et al.* [21] studied 245 women (175 with threatened miscarriage and 70 control). They concluded that the levels of progesterone together with beta-human gonadotropin could be convenient for predicting the outcome of threatened miscarriage. Mandira *et al.* [22] have concluded that the sensitivity and specificity of using β -HCG together with progesterone in detecting miscarriages may possibly reach 81 and 99%, respectively. Their results were similar to our results. They recommended that it is not more beneficial to use β -HCG together with progesterone rather than using each of them individually, as this provides no additional advantage in terms of increasing sensitivity.

Saleh *et al.* [23] concluded that although β -HCG was found to be more reliable than progesterone for the predication of threatened abortion, yet the assessment of β -HCG and progesterone together had no effect on sensitivity, whereas it increases specificity from 98.2 to 100%.

Similarly, Johns *et al.* [24] declared that the levels of both progesterone and free β -HCG, which represent independent variables, provide similar statistically significant values for miscarriage prediction. On the contrary, the individual use of each variable, that is, the level of either β -HCG or progesterone, could be beneficial for estimating spontaneous miscarriages during the first trimester, depending on the clinician's choice. Hence, progesterone level might be regarded as an acceptable parameter, rather than free β -HCG, because of its higher accessibility and cheaper cost.

On studying CA-125, we found that there was a statistical difference between the two groups, as it was higher in the aborted group. Mahdi [25], who estimated the level of CA-125 during the first trimester in women with threatened miscarriage, have concluded that the level of CA-125 cannot be regarded as a good predictor of the outcome of early pregnancy particularly in patients experiencing complicated vaginal bleeding. In contrast, the findings of this study disagree with those of our study, and hence such difference can be attributed to the small sample size used in their study. It has been found that women with threatened abortion had significantly higher levels of CA-125 (47.82 ± 30.93 vs. 30.08 ± 19.21 , $P=0.36$) [19].

Ayaty *et al.* [10] conducted a study comprising 100 women (50 women with healthy pregnancy as a control group and 50 women with threatened miscarriage as cases group) to assess the level of CA-125 and follow-up the pregnancy outcome. They found that the CA-125 level was significantly higher in the group with threatened miscarriage. These findings, which support our study, postulated that assessing the CA-125 level in the first trimester could be considered as a sensitive predictive tool for the fate of early pregnancy.

A previous study that was carried out by Mansy *et al.* [26] evaluated the effect of maternal serum β -HCG, progesterone, and CA-125 in predicting first-trimester miscarriage. Their study included 90 pregnant women recruited from the antenatal care clinic, El-Shatby Maternity University Hospital, Alexandria. The results of their study have revealed that 16.6% had aborted during follow-up; 60% of them had a history of

threatened miscarriage. The comparison of the studied groups has revealed that the calculated P value for serum β -HCG, progesterone level, and serum CA-125 was less than 0.001. These findings agree with us in the statistical difference between the two studied groups, but they were in disagreement with our work regarding the cutoff values among the three biochemical markers.

Consequently, we tried to add another biochemical marker to strengthen the predictive tools. In agreement with our idea, by adding serum level D-dimer, Zhou *et al.* [27] revealed in their meta-analysis that the determination of prethrombotic state-related indexes, including and D-dimer data, can be used as a basis for predicting recurrent spontaneous abortion in pregnant Chinese women.

Kawauchi *et al.* [28] found that D-dimer levels in pregnant women with threatened premature delivery and abortion progressively increase as gestational age increases. They also concluded that the appropriate D-dimer cutoff value might be useful in the detection of thrombosis. In contrast, Lugovsko *et al.* [29] found an insignificant difference in the mean values of D-dimer concentration, at various terms either normal pregnancy or pregnancy with risk abortion. Thus, soluble fibrin but not D-dimer quantification may provide useful diagnostic information at the pregnancy with repeated abortion. They reflected different point of view from our observations. Another recent study concluded that repeated assessment of D-dimer showed no clinical significance in the evaluation of thromboembolic events during pregnancy and attributed this to the biological fluctuation in D-dimer concentrations. D-dimer's sensitivity and specificity to predict severe preeclampsia during the third trimester were 94 and 67%, respectively. In addition, a higher cutoff of $1.94 \mu\text{g/ml}$ increases the specificity from 67 to 75%, whereas the sensitivity was maintained at 80% [30]. This resembles our observation regarding sensitivity and specificity.

Both the sensitivity and specificity of D-dimer levels for detecting thromboembolism range between 85–97 and 35–45%, respectively [31]. As the D-dimer level increases throughout pregnancy, a negative result with a sensitive test may be regarded as consistently resulting in excluding thrombus formation in pregnant women [32]. A recent study by Kawauchi *et al.* [28] found that D-dimer's sensitivity and specificity to detect thrombosis were 100 and 85.86%, respectively, when using a cutoff value of $4.8 \mu\text{g/ml}$. These results were in agreement with our findings.

Conclusion

During the first trimester, maternal serum markers such as β -HCG, progesterone, and CA-125 levels represent early, noninvasive, and fast techniques and are regarded as good predictors for the occurrence of miscarriage, and consequently the outcome of pregnancy. D-dimer can be considered as an additive biochemical tool in the early prediction of fetal wastage.

Acknowledgements

Author's contribution: All authors have read and approved the final manuscript. Sameh Salama: research idea, study design, manuscript writing, and data collection. Sondas M. Salem: manuscript writing and data collection. Mazen Abdel-Rasheed: data analysis and manuscript writing. Shereen Hamdy: analysis of blood sampling.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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