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The role of Quantitative ELABELA, β HCG, and Fibrinogen in Distinguishing Missed Miscarriage from Viable Pregnancy in Iraq

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ABSTRACT: Missed miscarriage (MM) is a prevalent obstetric complication in the first trimester of pregnancy. ELABELA (ELA), a G protein-coupled receptor that is expressed in the reproductive, cardiovascular, and renal tissues. Researches show the deletion of ELABELA in animal models has been demonstrated to produce preeclampsia like symptoms, underlining its importance in normal placental development. External administration of ELA has been demonstrated to enhance the invasiveness of extravillous trophoblasts and effect the morphological pattern of placental outgrowth, suggesting it plays a significant regulatory role in trophoblast differentiation and placentation. β -HCG is a glycoprotein hormone secreted by the syncytiotrophoblast cells of the placental tissue after implantation of a fertilized ovum and Fibrinogen (coagulation factor I) serving as the key structural protein responsible for blood clot formation and hemostatic integrity. The present study was carried out to evaluate and compare maternal serum concentrations of (ELA), β -HCG, and Fibrinogen between women with ultrasound confirmed missed miscarriage and gestational aged matched women with viable first trimester pregnancies (6 – 14 weeks), and using the ROC curve to investigate their ability to differentiate between the studied groups. We established that the mean serum levels of ELA, β HCG, and Fibrinogen were significantly lower in the Missed Miscarriage compared to viable pregnancy. Also, In the missed miscarriage arm it is the only primary peptide ELA that tracks plasma fibrinogen. We conclude that that combined panel (ELA, β HCG, and Fibrinogen) may have the potential to be used as an indicator of trophoblast health and placental function (ELA), failing pregnancy (Fibrinogen), and monitoring early pregnancy viability (β HCG) in missed miscarriage.

INTRODUCTION:

Spontaneous miscarriage, described as the unplanned termination of an intrauterine pregnancy prior to 20 completed weeks of gestation, is among the most frequently adverse outcomes observed in reproductive and clinical practice [1]. A first-trimester missed miscarriage is a type of spontaneous miscarriage in which the fetus or embryo has died without any associated uterine contractions or vaginal bleeding, represents a notable diagnostic issue, as it is often detected incidentally during routine ultrasound examination rather than through clinical symptoms [1].

This occurrence approximately 15–20% of reported pregnancies within the first and second trimesters [2]. A missed miscarriage in the first trimester can be described by an empty gestational sac on an ultrasound scan, an absence of fetal cardiac activity with a closed cervical upon clinical assessment, and an observation of minimal to no bleeding [2].

Socioeconomic factors have a significant impact on the incidence and severity of pregnancy related problems. Women from lower socioeconomic origins, notably those with manual vocations or unemployment, have considerably greater risks of stillbirth, preterm birth, neonatal mortality, and low birth weight than women in higher socioeconomic groups [3].

The causes of miscarriage are multifaceted and comprise immunologic, genetic, endocrine, uterine, infectious, and environmental factors. Chromosome abnormalities including aneuploidies and polyploidies are among the genetic causes, and they are especially prevalent in the first trimester. Whole exome sequencing has also identified other monogenic variations that are associated to pregnancy loss in later trimesters [4]. Female fertility diminishes considerably with age, resulting in longer pregnancy times and higher loss risks. Women aged 35-39.9 had twice the odds of miscarriage compared to those aged 30-34.9, and this risk more than quadruples for women aged 40 and above. Older paternal age (≥ 40 years) also increases miscarriage risk [5]. Approximately 23 million miscarriages happen worldwide each year, influencing over 10% of women at some time in their lives [6]. In addition to age, factors like body mass index (BMI) that is below normal both underweight and obese - raise the frequency of miscarriages and reduced fertility in both men and women [7].

ELABELA (also known as APELA or Toddler) is an endogenous peptide ligand first identified in 2013 from embryonic stem cells of zebrafish. In humans, it is encoded by the APELA gene, which produces a pre-proprotein of 54 amino acids. It exists in three biologically active isoforms (ELA-32, ELA-21, and ELA-11), which differ in length following post-translational cleavage of the precursor protein [8]. The APELA gene, responsible for encoding the ELA peptide, demonstrates a notable degree of evolutionary conservation across vertebrate species. In humans, it is situated at chromosomal locus 4q32.3 and comprises three distinct exonic units [9].

ELABELA can be found in the placenta, developing fetuses, and the cardiovascular system, where it is essential for gastrulation, angiogenesis, heart formation, and fluid homeostasis. In knockout mice, ELA deficiency causes severe cardiovascular abnormalities and early embryonic mortality, demonstrating its insufficient role in early organogenesis [10].

During gestation, ELA is synthesized by trophoblasts and syncytiotrophoblasts cell populations, exerting its biological effects upon fetal endothelial cells and adjacent trophoblasts through APJ receptor mediated signaling, thereby stimulating angiogenesis, vascular branching, and spiral artery remodeling crucial for adequate uteroplacental perfusion. Humans circulating ELA concentrations rise thought early pregnancy and reduction during late gestation, representing stage specific roles through implantation and early placentation rather than maintenance at term [10].

Recent study has additionally established that ELA protects trophoblasts and endothelial cells from oxidative stress and ferroptosis, which protect placental integrity and vascular perfusion. ELA regulate early placental and embryonic viability through a variety of mechanisms [11].

Human chorionic gonadotropin (HCG) is a glycoprotein hormone classified as heterodimeric. HCG comprises a 237 amino acid heterodimer with an α -subunit of 93 amino acids (14.5 k Da) and a β -subunit of 145 amino acids (22.2 k Da) [12]. β -HCG concentrations are assessed to roughly double every 48 hours, particularly in the early stages of a normally developing intrauterine pregnancies. Since the initial β -HCG concentrations and their progression of growth after a period of two days serve as helpful indicators for identifying and predicting pregnancy related results, serial β -HCG monitoring over a 48-hour interval is a well-established clinical tool for evaluating pregnancy viability [13].

Most viable intrauterine pregnancies show roughly a 66% growth in β -HCG concentrations, representing pregnancy development. If β -HCG concentrations do not rise over 50% within 48 hours, this indicates a nonviable pregnancy. This could be caused to early pregnancy loss or an ectopic gestation and necessitates immediate investigation [14].

Fibrinogen serves a critical function throughout pregnancy, playing a key part in maintain placental integrity. It also facilitates trophoblast growth and invasion throughout early pregnancy, as well as supporting the development of the maternal-fetal vascular interface [15]. Insufficient fibrinogen levels may raise the risk of placental abruption, retroplacental hematoma, or vaginal bleeding, complications that are usually seen in moderate to severe hypofibrinogenemia. In cases of dysfibrinogenemia, a remarkably high frequency of pregnancy loss has been recognized, principally among women carrying a thrombotic fibrinogen variant, whereas a similarly raised occurrence of postpartum hemorrhage has been detected in those with a bleeding phenotype [15]. Fibrinogen engagement of α IIB β 3 triggers PI3K signaling, which activates Rap1 for platelet spreading and mTORC2-dependent phosphorylation of Akt, a pathway required for trophoblast invasion and placental vascularization. Akt then phosphorylates GSK3, which enhances the thrombus formation and its stability. Activation of mTORC2 is PI3K β -independent, and the mTORC2/Akt pathway is not required for PI3K β -mediated platelet spreading [16].

METHODOLOGY:

This prospective case–control study was conducted between November 2025 and March 2026 in the Department of Chemistry and Biochemistry, College of Medicine, Al-Nahrain University, in collaboration with Al-Imamain Al-Kadhimain Medical City, Baghdad, Iraq. A total of 120 pregnant women aged 18–40 years were enrolled and equally allocated into two groups. The case group included 60 women with singleton pregnancies at 6–14 weeks of gestation diagnosed with missed miscarriage based on standardized ultrasonographic criteria demonstrating absent fetal cardiac activity, whereas the control group comprised 60 women with age- and gestational age-matched (± 1 week) viable singleton pregnancies confirmed by the presence of fetal cardiac activity. Eligible participants had a body mass index (BMI) below 40 kg/m² and provided written informed consent before enrollment. Women with multifetal pregnancies, threatened abortion or vaginal bleeding of other etiologies, uncontrolled diabetes mellitus, autoimmune disorders, hypertension, active infection, renal, hepatic, cardiac or thyroid diseases, polycystic ovary syndrome, or those receiving exogenous hormonal therapy or assisted reproductive techniques were excluded to minimize potential confounding factors affecting the investigated biomarkers. The required sample size of 60 participants per group was estimated using G*Power software (version 3.1), assuming a medium effect size (Cohen's $d = 0.80$), a two-tailed significance level of 0.05, and 95% statistical power, based on previously published first-trimester ELABELA data. Venous blood samples (5 mL) were collected from each participant under aseptic conditions. Approximately 2 mL was transferred into sodium citrate tubes for plasma fibrinogen determination, while the remaining blood was allowed to clot at room temperature for 20 minutes before centrifugation at 3000 rpm for 10 minutes to obtain serum. Serum samples were aliquoted and stored at -20°C until analysis. Serum ELABELA and β -human chorionic gonadotropin (β -hCG) concentrations were quantified using commercially available quantitative sandwich enzyme-linked immunosorbent assay (ELISA) kits (ELK Biotechnology, USA) according to the manufacturer's instructions, whereas plasma fibrinogen levels were measured using standard laboratory methods.

Statistical analysis:

Statistical analysis was performed using SPSS version 26.0 (IBM Corp., USA). Continuous variables were expressed as mean $\pm$ SD, and categorical variables as frequencies and percentages. Normality was assessed using the Kolmogorov–Smirnov test. Independent t-test and chi-square test were used for comparisons. Pearson correlation and multivariate logistic regression analyses were applied to assess associations and identify independent factors. A p-value < 0.05 was considered statistically significant.

Ethical approval:

The study was approved by the human ethics committee of Al-Imamain Al-Kadhimain Medical City, everyone who took part in the study was told about it and asked to sign a consent form. The patient was also guaranteed that his information would be kept private.

RESULTS

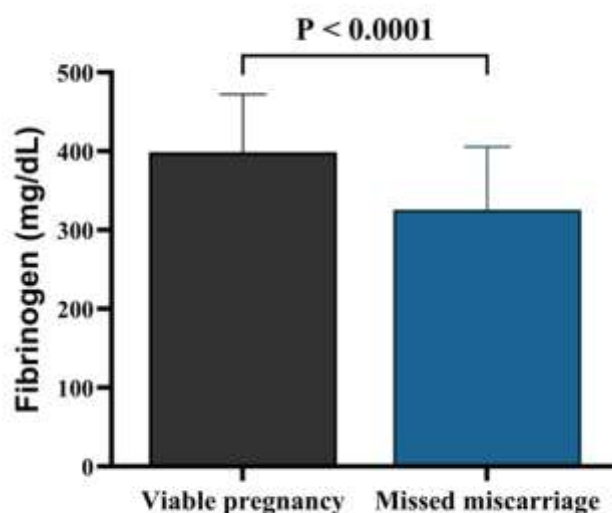
Comparison of fibrinogen levels between study groups.

Table 1: Association between Fibrinogen in groups of study

Lab. investigation	Group MM	Group VP	<i>P-value</i>
	<i>Mean ± SD</i>	<i>Mean ± SD</i>	
Fibrinogen level	325.70 ± 79.87	398.89 ± 73.50	p < 0.001

The statistical significance of the differences between study groups.

Figure 1: Bar graph comparing the levels of fibrinogen mg/dL by the study groups. The statistical significance of the differences between viable pregnancy and Missed Miscarriage is indicated above the bar.



Association of ELABELA and β -HCG levels between study groups.

Table 2: Comparison between serum ELABELA and β -HCG in groups of study.

Test result variables	Group MM	Group VP	<i>P-value</i>
	<i>Mean ± SD</i>	<i>Mean ± SD</i>	
ELABELA (ng/mL)	3.65 ± 1.90	12.99 ± 4.53	p < 0.0001
β -HCG (ng/mL)	17.34 ± 3.32	26.89 ± 8.06	p < 0.0001

The statistical significance of the differences between study groups.

Figure 2: Bar graph comparing the levels of β -HCG ng/mL by the study groups. The statistical significance of the differences between viable pregnancy and Missed Miscarriage is indicated above the bar.

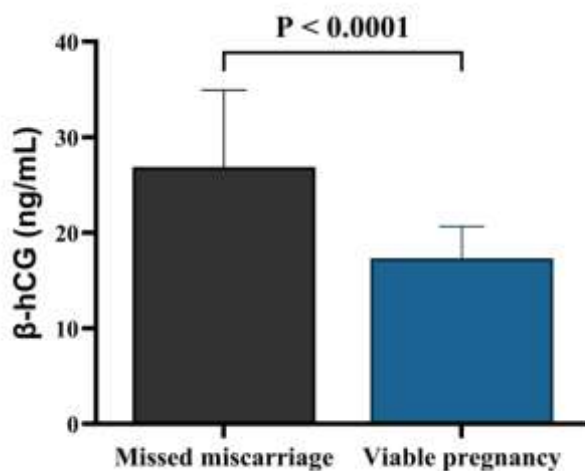
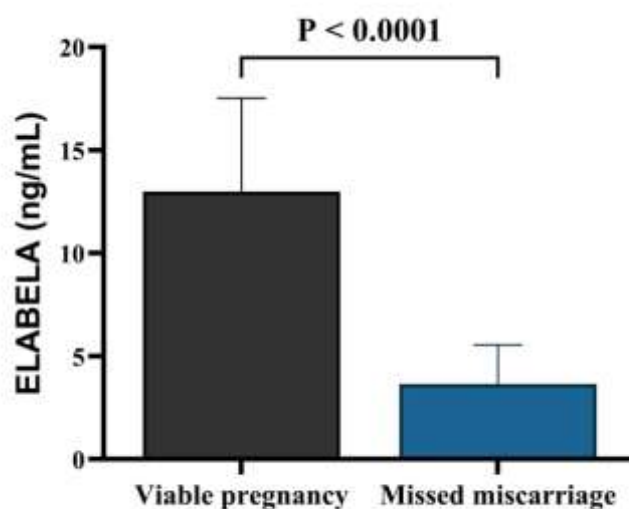


Figure 3: Bar graph that compares the levels of ELABELA ng/mL by the study groups. The statistical significance of the differences between Missed Miscarriage and Viable pregnancy is indicated above the bar.



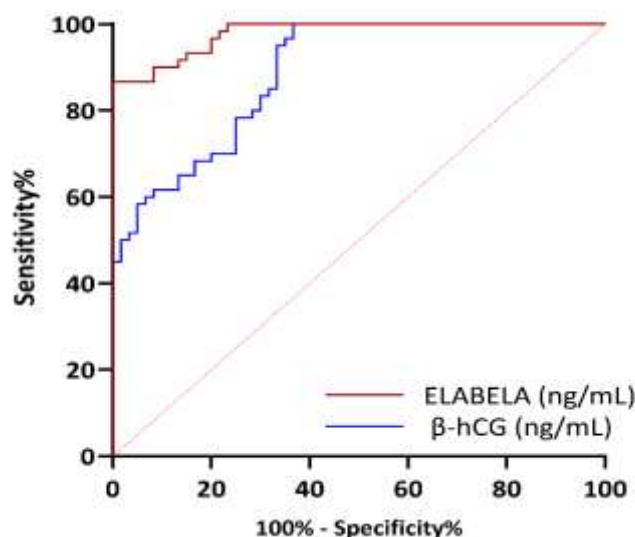
.Diagnostic performance of individual biomarkers

Table 3: The ability of ELABELA and β -HCG for correct diagnosis (Area Under the Curve) Cut-offs are expressed in the analyte's native units; LR+ values reported as " ∞ " reflect zero false-positive observations at the Youden-optimal threshold (Haldane–Anscombe-corrected LR+ = 105 for ELABELA and = 76 for β -HCG).

Test result variables	AUC (95 % CI)	Cut-off	Sens. (%)	Spec. (%)	LR+	LR-
ELABELA	0.978 (0.956–0.994)	< 5.51	86.7	100.0	∞ (no FP)	0.13
β -HCG	0.887 (0.826–0.936)	< 17.91	63.3	100.0	∞ (no FP)	0.37

ROC curve analysis for ELABELA and β -HCG levels.

Figure 4: ROC curve estimated the cutoff value for ELABELA and β -HCG along with their respective sensitivity and specificity.



Pearson correlations within the missed-miscarriage group

Table 5. Pearson correlation coefficients demonstrating interrelationships among fibrinogen, ELABELA, and β -HCG.

Variable	ELABELA		β -HCG	
ELABELA (ng/ ml)	r	1.00	r	0.04
	p		p	0.77
β -HCG	r	0.04	r	1.00
	p	0.77	p	
Fibrinogen	r	0.34	r	0.19
	p	0.01	p	0.16

DISCUSSION:

Our findings demonstrate a clear association between missed miscarriage and decreased fibrinogen levels, indicative of impaired normal placental hemostasis. An agreement was observed in a study conducted that serum fibrinogen levels were slightly but significantly decreased in the missed miscarriage group than that in the control group (MM: 4.31 ± 0.91 g/L; control: 4.44 ± 0.96 g/L; $P = .0084$) [17]. In the results of a study in 2026, a different result was observed that fibrinogen level was elevated in the group with missed abortion than that in the control group which received an induced abortion [18]. The discrepancies noted among the above studies may be attributed to the number of samples included in each study and some methodological aspects and specificity of the procedure, also the test combination and the screening timing during pregnancy affected the results. Elevation of fibrinogen is critical to the development of a prothrombotic state in pregnancy to counteract hemostatic challenges at delivery. Yet, pregnancy disorders with systemic inflammatory response syndrome may consume fibrinogen [19]. Fibrinogen has been reported to be essential to the maintenance of the placenta and early proliferation and migration of the trophoblast.

Severe or moderate hypofibrinogenemia or dysfibrinogenemia carriers, especially those carrying prothrombotic variants, are at a dramatically increased risk of miscarriage, because of low or dysfunctional fibrinogen. The incidence of miscarriage in this group is reported to be between 20% and 50% [20]. Experimental study conducted in mice and models of uteroplacental attachment demonstrates that maternal fibrinogen assists in preserving hemostatic balance and stabilize placental-maternal attachment, which prevents bleeding and separation at the implantation site [21]. Placental pathological studies in fibrinogen conditions demonstrate fibrin deposits within maternal fetal interface, in addition to ischemic lesions, showing impaired local hemostasis and micro thrombosis [22]. The present study found a significant difference in the mean β -HCG levels between groups, with women in the case group exhibiting significantly lower β -HCG levels than those in the viable pregnancy group ($p = 0.0001$). Hassan et al. agreed with this study which showed a significant difference in the mean of β -HCG concentrations between groups, with women in the missed miscarriage group showing significantly lower β -HCG concentrations compared to the viable pregnancy group ($p = 0.038$) [23]. Also, Abbara et al. agreed with this result as they reported that plasma β -HCG concentrations peaked approximately eight weeks of pregnancy and had been significantly reduced in miscarriages across most gestational ages. The Abbara et al. performed ROC analysis to compare plasma levels in healthy and miscarried pregnancies. β -HCG had an AUC accuracy of 0.859 (95% CI: 0.82-0.899) [24]. In most early pregnancies, a low absolute β -HCG or a slow increase is frequently linked to an adverse outcome [25]. In women affected by early missed miscarriage β -HCG and VEGF serum levels were diminished along with the down-regulation of villous VEGF-MEK/ERK signaling and microvascular density, indicating that decreased β -HCG production leads to impaired villous angiogenesis [26]. The variability in sensitivity and specificity of β -HCG reported in the above-mentioned studies may be explained by those studies processing, methodology, and sampling time differences. In addition, the high or low cut-off values reported in different studies may be associated to the different gestational age, or to the duration of miscarriage. Human chorionic gonadotropin is a very well-studied parameter for early pregnancy outcome. It counts as non-diagnostic when used as a single value. Serial measurements of serum HCG can detect pregnant women who need further surveillance for early pregnancy demise. The present work showed the Mean Serum levels of ELABELA were significantly lower in missed miscarriage. Retrospective case-control study ($n = 108$ healthy controls vs 25 MA patients) agreed with this study as they estimate that plasma ELA examined by ELISA and noticed that in healthy pregnancies, ELA increases in early and mid-gestation before decreasing in late pregnancy. During same earlier gestation stages, maternal serum ELA levels were considerably lower in missed abortion patients (4.59 ± 1.23 ng/mL) compared to healthy women (5.77 ± 1.21 ng/mL, $p < 0.01$) [27]. ELABELA is produced in the placenta (particularly first trimester trophoblast) for increases trophoblast proliferation, migration, and extravillous trophoblast invasion, which leads to appropriate placental anchoring and spiral artery remodeling [28]. ELA also triggers APLNR signaling during early gestation, promoting angiogenesis and embryonic survival [29]. Low ELABELA levels have been reported in several placental insufficiency conditions, including intrauterine growth restriction (IUGR), suggesting that ELA deficiencies may indicate poor trophoblast activity and perfusion. It was previously shown that ELABELA deficient pregnant mice had placental insufficiency of vascular origin [30]. In human embryonic stem cells, ELA enhances self-renewal and growth via activating the PI3K/AKT signaling pathway [31]. In the Pearson correlation analysis used in this study, ELABELA's behaviors deserve a closer look. In the missed miscarriage arm it is the primary peptide that tracks plasma fibrinogen ($r = 0.34$; $p = 0.01$). The simultaneous reduction of ELABELA and fibrinogen in missed miscarriage may reflect the simultaneous disruption of two upstream inputs, APJ-dependent and integrin α IIB β 3-dependent modes of input delivery to a convergent PI3K/Akt/GSK3 signaling module important for trophoblast invasion, survival, and placental vascular remodeling. Rather than one being a consequence of the other, their dual decrease more likely represents a systemic placental-vascular failure, wherein the paracrine peptide axis (ELABELA/APJ) and the extracellular matrix adhesion axis (fibrinogen/integrin) are compromised simultaneously, culminate in an exponential down-regulation of PI3K/Akt signaling below that required for sustaining a successful placentation. In the opposing, ELABELA showed no significant correlation with β -HCG ($p = 0.77$).

CONCLUSION:

Collectively, these findings suggest that ELABELA is more sensitive than β -HCG for predicting missed miscarriage but they have similar specificity. A positive correlation was found between ELABELA and fibrinogen in prediction of missed miscarriage, whereas ELABELA did not correlate with β -HCG. Variability among studies may be attributed to differences in methodology, sampling time, different gestational age, and population characteristics. ELABELA and fibrinogen are novel, noninvasive, early, rapid and excellent predictors of missed miscarriage; they may be utilized, if confirmed by further studies.

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