Using Multiple Serum Biomarkers in Detecting the Outcome of Threatened Miscarriage

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Abstract:

Background: Threatened abortion is presumed when there is a bloody vaginal discharge or bleeding through a closed cervical os. cancer antigen 125 (CA-125), B-Human chorionic gonadotropin (B-hCG), and Soluble vascular endothelial growth factor receptor (sVEGFR-1 or sFlt-1R) are biochemical markers that have been studied to establish if they can predict the outcome of threatened miscarriage.

Methods: A prospective observational study that was conducted at the Department of Obstetrics and Gynecology at Azadi Teaching Hospital/ Kirkuk-Iraq, over a period of eight months from first of April 2019 till first of December 2019. It included 96 pregnant women at 7 – 13 weeks of gestation with singleton pregnancy, viable fetus, and closed cervical os they presented with signs and symptoms of first trimester threatened miscarriage. After the first visit, follow up was done until they passed into the second trimester of pregnancy, and patients from the study group were divided into group 1: Included 19 patients who ended with miscarriage and group 2: Included 69 women who continued their pregnancy into the second trimester.

We compared the level of the Cancer antigen 125 (CA-125), B-Human chorionic gonadotropin (B-hCG), and Soluble vascular endothelial growth factor receptor (sVEGFR-1 or sFlt-1R) between the two study groups to assess their utility for prediction of the outcome of first-trimester threatened miscarriage.

Results: Mean of CA 125 marker was significantly higher in participants who ended with miscarriage than that in participants who continued to second trimester. Means of B-hCG and sFlt-1markers were significantly lower in participants who ended with miscarriage than that in participants who continued to second trimester Serum CA-125 marker > 38.8 IU/ml, Serum β-hCG marker < 20211.3 mIU/ml, and serum sFlt-1 marker < 1731.7 pg/ml are predictors for risk of miscarriage.

Conclusion: Serum CA 125, B-hCG, and sFlt-1 biomarkers represent non-invasive, early, fast and excellent predictors of pregnancy outcome in women with threatened miscarriage. Taking into account the feasibility and cost, using serum β-hCG instead of the more accurate one (i.e. serum sFlt-1) would be more logical decision. Further studies are needed in this field.

Keywords: Biomarker; Miscarriage; CA 125; β-hCG; sFlt-1; Pregnancy.

Introduction:

Threatened miscarriage is defined as vaginal bleeding in the presence of a viable pregnancy prior to 23 weeks and 6 days of gestation [(1)]. Miscarriage is common, occurring in at least 15–20% of pregnancies. Possibly up to 40% of all conceptions. It includes all pregnancy losses before 24wks,the vast majority are before 12wks[(2)]. After the 1st trimester, both the abortion rate and the incidence of chromosomal anomalies decrease [(3)]. As a group,

miscarriage can be divided clinically several ways. Commonly include threatened, inevitable, incomplete, complete, and missed abortion[4].

Among women with threatened miscarriage, as not all are at equal risk of losing the pregnancy. Individualizing outpatient management based on an initial risk evaluation would be a boon to clinical care and suggest any additional therapy [5]. Focus has been made on identifying serum biological markers for the prognosis of threatened spontaneous miscarriage. A meta-analysis investigating biomarkers to determine pregnancy outcome for women presenting with threatened miscarriage have showed conflicting results with the need for larger studies and further validation [6]. Other studies have looked at various biomarkers such as serum beta- HCG, estradiol, inhibin, CA 125 as well as progesterone. Ultrasonography, serial serum quantitative assessment of B-subunit of human chorionic gonadotropins ((β-hCG)), serum cancer antigen -125 (CA-125) and serum progesterone values measured alone or in various combinations, have proven helpful in ascertaining if a live intrauterine pregnancy is present [3]. As far as we know, there is no such study in our city Kirkuk and/or Iraq.

Many studies found that miscarriage associated with an adverse outcome, like [7-9]:

- Adverse obstetric outcomes, such as antepartum hemorrhage, preterm delivery, cesarean delivery, preterm premature rupture of membrane.
- Pregnancy-induced hypertension, preeclampsia, placenta previa, and placenta abruption.
- Adverse perinatal outcomes, such as perinatal death, small-for-gestational-age infants and low birth weight.

CA 125 also known as mucin 16 or MUC16 is a large membrane glycoprotein belonging to the wide mucin family, encoded by the homonymous MUC16 gene. It was first described in 1983 as a biomarker for epithelial ovarian cancer (EOC). Since, it is increasingly used alone or in combination with other markers with or without pelvic ultrasound for the diagnosis of EOC [10].

CA-125 might have a role in the preparation of the endometrium for successful implantation [11]. More trophoblastic damage is associated with higher levels of CA125 and lactate dehydrogenase (LDH). CA-125 can be used as a prognostic factor to the outcome of pregnancy as it might be related to the extent of trophoblastic destruction [12].

Human chorionic gonadotropin (hCG), also defined as “the hormone of pregnancy” which has a significant role in human reproduction. A variety of studies demonstrated its vital role in establishing and maintaining pregnancy, via placentation and early embryo development [13].

The concentration of hCG gradually elevated during early pregnancy until it peaks at about 8 to 10 weeks of gestation, after that falling to a stable new level for the rest of pregnancy. It is known that subnormal values of hCG are associated with a failing pregnancy or a miscarriage. It has also been hypothesized that hCG may be a placental link for the development of local maternal immunotolerance[14, 15].

(sFlt-1or sVEGFR-1) isa tyrosine kinase protein

with antiangiogenic properties. A non-

membrane associated splice variant of VEGF receptor 1 (Flt-1)'
During fetal and placental development, one of the most important factors is angiogenesis. It is mainly regulated by pro-angiogenic and anti-angiogenic factors. Vascular endothelial growth factor (VEGF) and placenta growth factor (PlGF) play major roles within this process, especially in the stabilization of endothelial cells in mature blood vessels. This finding suggests that sFlt-1R-1 may be a potential biomarker for indicating early pregnancy loss [16, 17].

Aim of study

To evaluate the role of biomarkers (CA-125, β-hCG and sFlt-1 receptor) in predicting the outcome of threatened miscarriage.

Patients and methods:

This prospective observational study was conducted at the Department of Obstetrics and Gynecology at Azadi Teaching Hospital / Kirkuk-Iraq over a period of eight months from 1st of April 2019 till 1st of December 2019. The study protocol was approved by the above-mentioned hospital's ethical committee and permission from hospital's administration was obtained before initiating the study.
The study included 96 pregnant women (who attend the outpatient clinic or emergency department of Azadi hospital) between (7 – 12 weeks +6days) of gestation with singleton pregnancy, viable fetus, vaginal bleeding and closed cervical os. Gestational age was calculated at the time of presentation according to the first day of last menstrual period and confirmed by transabdominal ultrasound examination.

The **exclusion criteria** were as follow:
Inability to give written consent, blighted ovum. Ectopic pregnancy, hydatidiform mole. History of abnormal uterus, previous miscarriage, multiple pregnancies. History of medical disease (Diabetes or thyroid disease). Presence of local gynecological disease (Fibroid or adnexal masses verified by normal appearance of the uterus and ovaries by ultrasound). Presence of local cervical and vaginal disease. Malignancy (ovary, lung, pancreas, and colon).
All study participants were subjected to the following:

1. Detailed history according to a questionnaire which included information about: Demographic characteristic, Obstetrical history: (Gravity, parity, last menstrual period, and gestational age), Gynecological history: History of (uterine fibroid, ovarian cyst), Past medical history, chronic medical diseases, Past surgical history, previous gynecological surgeries, Drug history.
2. Clinical examination: Physical examination (general examination, vital signs), Abdominal examination, Gynecological examination:

- Inspection of the perineum for the amount of bleeding, signs of trauma or lesions to detect any abnormalities, infections or ulcer).
- Speculum examination to localize the bleeding origin: Vagina, cervix, uterus, quantify the bleeding; inspection of the cervix for the presence of polyps, ulcers or other lesions.
- Pelvic examination for uterine size and cervical dilatation.

3. Examination by imaging

Abdominal ultrasound: All women were examined by two Dimensional abdominal ultrasounds to confirm intrauterine pregnancy, assessment of

the number of fetuses, viability, and presence/absence of sub-chorionic hematoma. Excluding an ectopic pregnancy, pelvic mass, adnexal mass, fibroid and free fluid.

4. Lab rotary investigations

Peripheral Venous blood samples (5ml) were collected at admission from all participants. About 3 ml blood was allowed to clot and the sera were separated after centrifugation at 2000-3,000 RPM (revolution per minute) for 10 minutes and used for biochemical investigations by storing it at 2-8ºc for 24 hours. The remaining 2 milliliters of whole blood were used for complete blood count and blood group and Rhesus;

a. CA 125

The test was performed on the serum of the study population by the fully automated Mini-Vidas® machine (Biomerieux®, France) using its custom kit. The assay principle combines a 2-step enzyme Immunoassay sandwich method with a final fluorescent detection (ELFA).

b. **β-hCG**

Measurement of β-hCG in the subject's serum is similar to CA-125 using the same machine applying the same principle with specific kit for β-hCG. The assay was ELFA that was performed in an automated instrument.

c. **Soluble vascular endothelial growth factor receptor1 (sFlt-1)**

The level was measured applying the Enzyme linked Immunosorbent Assay (ELISA) principle using Human SVEGFR1 ELISA kit (Catalogue No: RDEEH0024, Canada) according to manufacturer instructions using ELISA machine system (BIOTECH Elx 800/USA) at a private laboratory.

After the first visit, follow up done by contact with each participant by cell phone call conversation until they passed into 2nd trimester of pregnancy, and at that time patients from the study group were divided into:

Group 1: Included 19 patients who ended with a miscarriage.

Group 2: Included 69 women who continued their pregnancy and proceeded into the second trimester.

We compared the level of the tested biochemical marker between the two study groups to assess their utility for prediction of the outcome of first-trimester threatened miscarriage.

Statistical analysis:

The data analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Independent t-test (two-tailed) was used to compare the continuous variables accordingly. Receiver operating characteristic (ROC) curve analysis was used for prediction of serum CA 125, β-hCG and sFlt-1 markers level as a predictor for a risk of miscarriage. A p-value <0.05 was considered significant.

Results:

The study included initially 96 pregnant women and five of them showed invalid or missed B. HCG, CA125, or sFlt-1 results, and three participants were lost from follow up, so the total number of participants included in the analysis was 88. All of them were presented with signs and symptoms of 1st trimester threatened miscarriage. The mean age of the participants was 24.81 ± 6.5 years and the mean gestational age was 10.41 ± 1.4 weeks,distribution of study

participants by general characteristics shown in table1.

Comparisons of the study serum biomarkers between group 1 and 2 are shown in Table 2. Although serum CA 125 level was higher in group 1, the serum β-hCG and serum sFlt-1 levels were higher in group 2 (63.42 ± 16.4 versus 31.28 ± 10.8 IU/mL, 17331.2 ± 2319.4 versus 57216.5 ± 9534.8 mIU/mL, and 982.4 ± 231.5 versus 2731.7 ± 533.1 pg/mL, respectively, p=0.001, all).

ROC analysis cut-off points, sensitivity, specificity, positive and negative predictive values (PPV, and NPP) results of the above-mentioned 3 parameters are shown in Table 3, and Figures 1, 2, and 3. The area under curve (AUC) values for cut-off >38.8 IU/mL of CA125, < 20211.3 mIU/mL of β-hCG, and <1731.7 pg/mL of sFlt-1 in predicting miscarriage were 85.7%, 87.8%, and 90.3%, respectively.

There were no statistically significant correlations detected between all biological markers and both of maternal age and gestational age P>0.05).

Table (1): Distribution of study participants by general characteristics.

Variable	N= 88	Percentage (%)
Age (Years)		
< 20	17	19.3
20 – 29	51	58.0
≥ 30	20	22.7
Mean ± SD	24.81 ± 6.5	
Gestational age (Weeks)		
$7 – 8^{+6}$	18	20.5
$9 – 10^{+6}$	39	44.3
$11 – 12^{+6}$	31	35.2
Mean ± SD	10.41 ± 1.4	
Parity		
Nulliparous	22	25.0
1 – 3	41	46.6
> 3	25	28.4

Table (2): The mean serum level of the three biomarkers (CA125, B-HCG and sFIt) in the studied groups.

Serum biomarkers	Pregnancy outcome group		P – Value
	Miscarriage Mean ± SD	continued pregnancy to second trimester Mean ± SD	
CA 125 (IU/mL)	63.42 ± 16.4	31.28 ± 10.8	0.001
β-hCG(mIU/mL)	17331.2 ± 2319.4	57216.5 ± 9534.8	0.001
sFlt-1 (pg/mL)	982.4 ± 231.5	2731.7 ± 533.1	0.001

Table (3): Diagnostic accuracy of serum CA 125, (β-hCG) and sFlt-1 biomarkers for risk of miscarriage.

Serum biomarkers	Cut-off value	Sensitivity	Specificity	PPV	NPV	Accuracy
CA 125 (IU/mL)	38.8	89.5%	73.8%	50.5%	95.7%	79.3%
β-hCG(mIU/mL)	20211.3	78.9%	94.2%	78.9%	94.2%	90.9%
sFlt-1 (pg/mL)	1731.7	84.2%	81.2%	55.2%	94.9%	81.8%

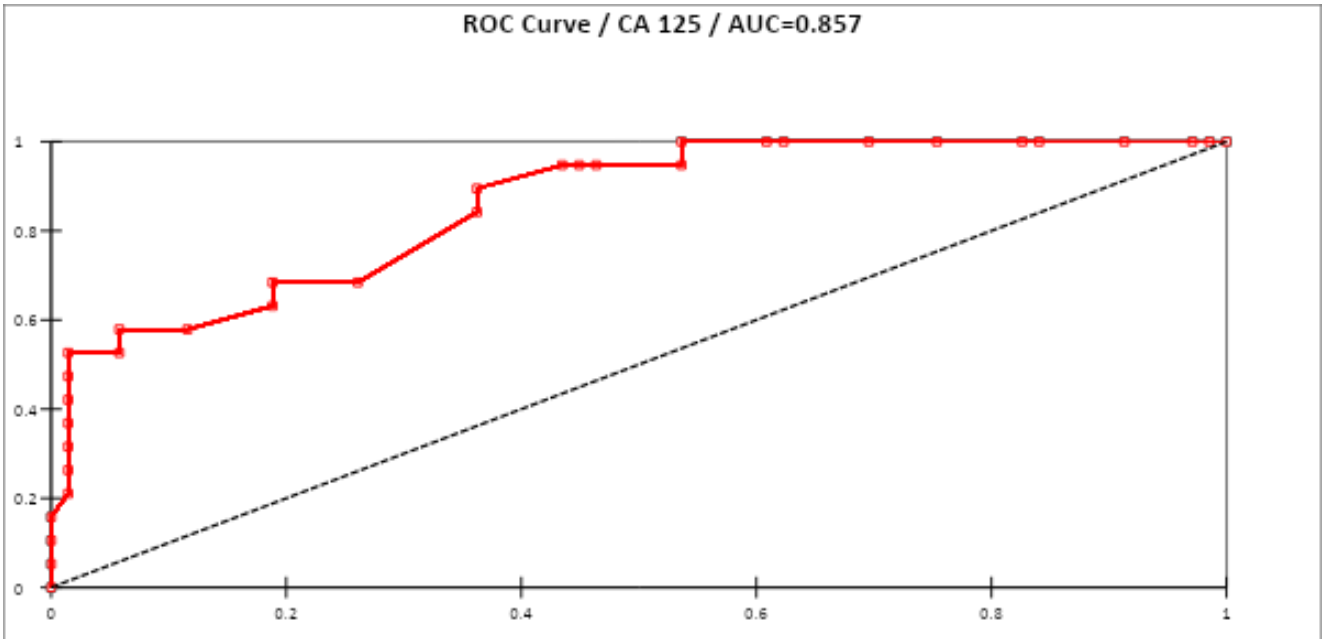

Figure (1): ROC curve for serum CA 125 marker as a predictor for risk of miscarriage.

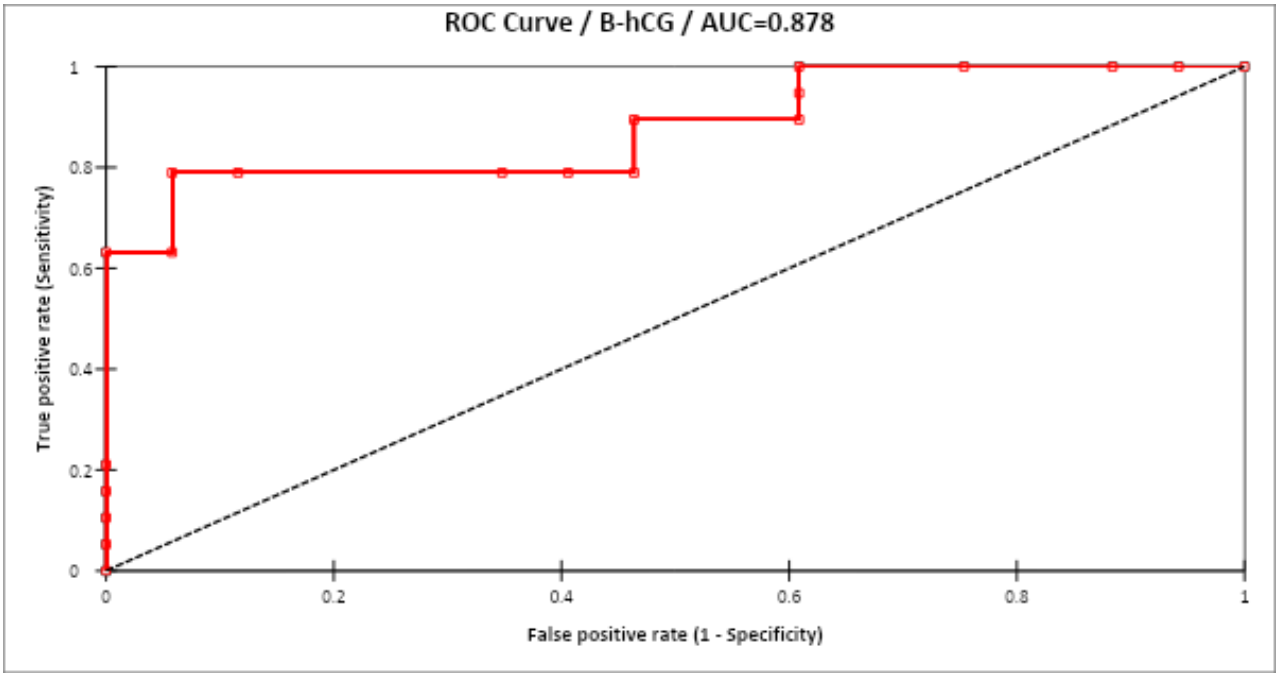

Figure (2): ROC curve for serum β-hCG marker as a predictor for risk of miscarriage.

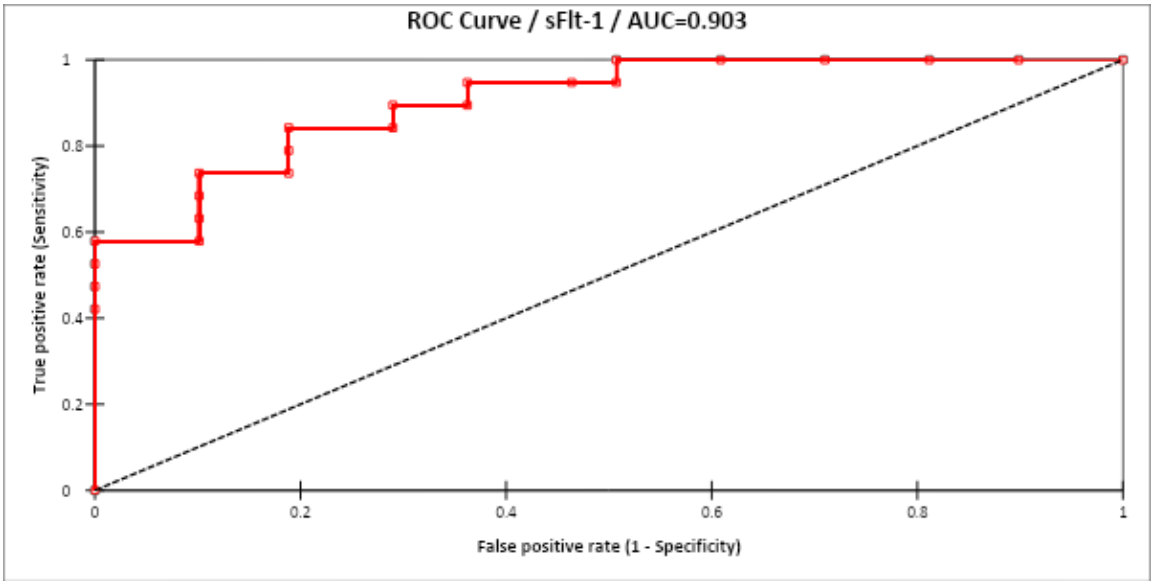

Figure (3): ROC curve for serum sFlt-1 marker as a predictor for risk of miscarriage.

Discussion:

Threatened miscarriage can be a distressing experience for the pregnant women.

It is common in early pregnancy and an estimated 15% to 20% of clinical pregnancies miscarry.

Often the expectant approach adopted is not appreciated and more active treatment is expected or even demanded by couples [18].

In the present study, mean of CA 125 marker was significantly higher in patients ended with miscarriage than those who continued with ongoing pregnancy (63.42 versus 31.28 IU/ml, P= 0.001).

Furthermore, Receiver operating characteristic (ROC) curve analysis was constructed for serum CA 125 and the cut-off point of CA 125 marker was 38.8 IU/ml, so serum CA 125 marker > 38.8 IU/ml is predictive for risk of miscarriage as a large significant area under the curve (AUC= 85.7%) indicating significant association between higher level of serum CA 125 marker and risk of miscarriage. Serum CA 125 marker concentration was 89.5% sensitive, 73.8% specific, and 79.3% accurate as a marker for risk of miscarriage.

in comparison to other studies, a comparable result observed in a study conducted by El Dien and colleagues[19] in 2019, in which 76 women with threatened miscarriage were enrolled and divided into, group I: patients who miscarried (17 patients) and group II including those who continued their pregnancy (59 patients). Results obtained in regard to biochemical markers revealed a statistically significant difference between the two groups in regard serum CA 125 levels, as it increased significantly in group I (68.05±8.71 vs. 26.36±1.29, P <0.001). On the other hand, the cut-off point of CA 125 marker was >37.2 IU/ml, so serum CA 125 marker > 37.2 IU/ml is predictive for risk of miscarriage, it was 86.0% sensitive and 84.0% specific for risk of miscarriage.

In contrary, Mahdi and colleagues[20] in their study in 2010, observed no significant difference between groups I who end with miscarriage and group II that had ongoing pregnancy in spite of its higher values (39.9±15.4, P>0.05). Mahdi's results were in accordance with that observed in Osmanağaoğlu et al study in 2010, in which 140 singleton pregnant women were included as Group

I (n=21) who resulted in miscarriage; Group II (n=129) included normal pregnancies. Both groups were compared statistically, in which no significant difference was found in terms of mean CA125 values between them (p>0.05)[21].

Differences observed among above mentioned studies can have attributed to many factors, as the sample size of each study, which can have determined the type of association. . Regarding the mean of β-hCG marker in the current study, it was significantly lower in aborted patients than that in participants who continued with ongoing pregnancy (17333.2 versus 57216.5 mIU/ml, P= 0.001).

Furthermore, (ROC) curve analysis was constructed for serum β-hCGand the Cut-off point of serum β-hCGmarker was 20211.3 mIU/ml, so serum β-hCGmarker < 20211.3 mIU/ml is predictive for risk of miscarriage, indicating significant association between lower level of serum β-hCGmarker and risk of miscarriage. Serum β-hCGmarker concentration was 78.9% sensitive, 94.2% specific, and 90.9% accurate as a marker for risk of miscarriage.

In comparison to other studies, a comparable result observed in El Dien et al[19] study in 2019, in which 76 women with threatened miscarriage were enrolled and divided into those aborted (group I) and those continued their pregnancy (group II). Results obtained showed that statistically significant difference between the two groups in regard to serum β-hCGlevels, as it significantly decreased in group I (12.68±2.60 vs. 71.13±5.21, P <0.001), furthermore, the Cut-off point of serum β-hCGmarker was <19.4ng/ml so serum β-hCGmarker <19.4ng/ml is predictive for risk of miscarriage with sensitivity and specificity were 80.0% and 78.0% respectively.

Another comparable result observed in Osmanağaoğlu et al[20] study in 2010, in which 140 singleton pregnant women were included and divided into Group I (n=21) who resulted in miscarriage; Group II (n=129) included normal pregnancies. Both groups were compared statistically and found that difference was found in terms of (β-hCG) as it decreased significantly in group I. Furthermore, the cut-off point of serum β-hCGwas 20 ng/ml, so serum β-hCGmarker <20ng/ml predictive for risk of miscarriage with sensitivity and specificity were 91.0% and 82.0% respectively.

Furthermore, De Leon and colleagues[58]in their study in 2004, stated that only the group of women who experienced miscarriages had significantly lower serum levels of beta-hCG at the 10th-14th week of gestation (P<0.03).

In the current study, mean of sFlt-1 marker was significantly lower in participants who ended with miscarriage than that in participants who continued into second trimester (982.4 versus 2731.7 pg/ml, P= 0.001). Furthermore, (ROC) curve analysis was constructed for serum sFlt-1 marker and the cut-off point of serum sFlt-1 marker was 1731.7 pg/ml, so serum sFlt-1 marker < 1731.7 pg/ml is predictive for risk of miscarriage, indicating significant association between lower level of serum sFlt-1 marker and risk of miscarriage. Serum sFlt-1 marker concentration was 84.2% sensitive, 81.2% specific, and 81.8% accurate as a marker for risk of miscarriage.

Similarly, Chai and colleagues[22] found in a study done in 2013, that both protein and mRNA expressions of sFlt-1

in the miscarriage group were significantly lower than in the normal pregnancy group ($P < 0.01$). Another comparable result observed in Muttukrishna et al [23]study in 2011, in which found that mean sFlt-1 levels were significantly (86% decrease, P<0.001) lower in the threatened miscarriage subgroup with a subsequent miscarriage compared to asymptomatic controls, suggesting these proteins are sensitive predictive markers of subsequent pregnancy loss,and showed that O2 concentration in the placental bed blood is inversely related to sFlt-1 in early pregnancy ,a decreased level of sFlt-1 in maternal serum prior to miscarriage suggests that impaired placentation may be associated with placental metabolic changes before the appearance of clinical symptoms of miscarriage and these changes are modulated by an abnormal increase in O2 concentration inside the placenta after implantation.

In comparison to other studies, different results observed in Keskin et al [16] study in 2015, in which they noticed that sFlt-1 levels were significantly elevated in pregnant women with threatened miscarriage compared to pregnant women without 1st trimester bleeding (39.10 vs. 5.24 (ng/ml), P= 0.001).

Differences observed can attributed to two important factors, first sample size enrolled in each study and the history of previous pregnancy loss. In fact, during fetal and placental development, one of the most important factors is angiogenesis. It is mainly regulated by pro-angiogenic and anti-angiogenicfactors. So free VEGF and free PlGF may play a role in trophoblast proliferation and vascular formation [17].

Conclusion:

Serum CA 125, (β-hCG) and sFlt-1 biomarkers represent non-invasive, early, fast and excellent predictors of pregnancy outcome in women with threatened miscarriage.According to individual differences between biomarkers in sensitivity, specificity, and predictive values, we can prioritize which marker to use according to availability, price with the most accurate one being β-hCG having promising result with regard to its availability and easiness.

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