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Comparison of Levels of Activin A and Follistatin in Ectopic Pregnancies and Missed Abortions Patients

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ABSTRACT

Background & Objective: Activin A, a protein in the TGF-β superfamily, plays a crucial role in reproductive regulation by regulating FSH secretion and activating intracellular signaling pathways. Follistatin regulates FSH secretion, affecting follicle genesis and ovulation, playing a crucial role in reproductive processes, especially in ectopic pregnancy and missed abortions. Missed abortions are often caused by genetic factors like chromosomal abnormalities and maternal hormonal imbalances. Evaluated the blood levels of follistatin and activin A in women diagnosed with ectopic pregnancy and missed miscarriage. Research into how follistatin and activin A regulate physiological processes.

Materials & Methods: The study included 120 women between the ages of 18 and 45 years, divided into three groups: normal pregnancies (60 women), ectopic pregnancy (30 women), and missed miscarriage (30 women), the gynecology clinic of Baghdad Teaching Hospital for the period from Sept 2023 to Jan 2024.

Results: Activin A and follistatin significantly higher in women with ectopic pregnancy and missed abortions than in the control groups. In addition, compared to patients in the missed abortion group, the ectopic group's incidence was significantly lower.

Conclusion: Serum Activin A and Follistatin levels can be used as indicators of ectopic pregnancy and missed abortion. Serum FST level at cut-off (>5.24) can be used as a novel biomarker of women with missed abortions. Activin A is involved in the regulation of ovarian follicle development and corpus luteum function in females.

Keywords: Activin A, Follistatin, Body Mass Index, Missed Abortions, Ectopic Pregnancies

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Introduction

Missed abortion (MA) It is a form of miscarriage with several etiological causes that occurs when the retained intrauterine product of gestation fails to escape naturally, resulting in fetal mortality **(1)**. GTN, a rare and severe pregnancy problem, includes various tumor types resulting from poor trophoblastic tissue proliferation, including choriocarcinoma, epithelioid trophoblastic malignancies, and hydatidiform lesions **(2)**. Miscarriage is associated with sperm quality, environmental factors, endocrine diseases, thrombophilia's, and defects in the anatomy of the uterus, reproductive immune disorders, and embryonic chromosomal abnormalities **(3)**. Patients may show up with mild clinical signs like vaginal bleeding or stomach ache, or they may not. About 8–20% of clinically diagnosed intrauterine pregnancies result in missed abortions **(4)**. Eighty percent of miscarriages occur in the first 12 weeks of pregnancy, and after this week, the risk of miscarriage gradually decreases **(5)**.

Ectopic pregnancy (EP) is an important cause of several maternal morbidities. 2% of reported pregnancies are EP **(6)**. Ectopic pregnancy, involving fertilized eggs in the tube outside the uterus, accounts for 1%-2% of spontaneous pregnancies globally but is a leading cause of morbidity and maternal death **(7)**. The fallopian tube is responsible for 90% of all ectopic pregnancies, with the ampulla parts accounting for 80% of these cases **(8)**.

Serum indicators other than Beta-hCG are being investigated as possible diagnostic tools; in particular, pregnancy-associated plasma protein A and activin-AB show promise **(9)**. Smoking, in vitro fertilization (IVF), and tubal damage from pelvic infections or prior adnexal operations are the most identified risk factors for ectopic pregnancy **(10)**.

The following are risk factors for tubal ectopic pregnancy (TEP): endometriosis, smoking, pelvic inflammatory disease, genetic uterus defects, fallopian

tube surgery, infertility, and pelvic or abdominal surgery **(11)**.

Activin-A was initially classified as a gonadal protein that stimulates the pituitary's production and release of the follicle-stimulating hormone **(12)**. It is well known that activin A and the receptors for it are expressed in the female uterus and placenta **(13)**.

In the USA, one to two percent of all first-trimester pregnancies result in an ectopic pregnancy. This small share accounts for 6% of all pregnancy-related deaths **(14)**. When not becoming pregnant, activin Many reproductive tissues, such as the pituitary gland, ovary, uterus, testis, and epididymis, have been shown to secrete something **(15)**. FSH (Follicle-stimulating hormone) synthesis is typically inhibited through a protein called follistatin (FST), which's predominantly created and produced by the liver **(16)**.

A protein called glycosylated plasma is linked to the transforming growth factor group

(17). The amino acid follistatin binds to components of the transformed growth factor-β (TGF-β) group and controls their biological function **(18)**. FST levels were determined in eumenorrheic women during the follicular and luteal phase of the menstrual cycle **(19)**.

Follistatin expression is reduced in placental trophoblasts and maternal serum in PE patients and early-onset severe PE, but its function in preeclamptic placentas with FST deficit remains unknown **(20)**.

Methods

Serum investigations included serum activin A and serum Beta-hCG measured using ELISA. The data was analyzed using SPSS Version 25.0 software (IBM, USA), with graphs and statistical tests such as t test, chi-square test, Pearson correlation coefficient, and ROC test. A P value of less than 0.05 was considered significant. A case-control study was conducted in the gynecology wards of the Baghdad teaching hospital/medical city. The study included 120 women aged 18–45 years, 30 of whom were diagnosed with missed abortion, 30 had ectopic pregnancy, and the other 60 were in the control group.

Results

The study had 120 participants, of whom 60 (49.2%) were healthy controls, 30 (25%) had an ectopic pregnancy, and 30 (25%) had a missed abortion.

A significant difference of Activin-A mean ± SD between the three groups, p-value < 0.001. The control group had significant lower mean ± SD of Activin-A (773.56 ± 130.26 pg/ml) in comparison to the ectopic group (1408.06 ± 219.02 pg/ml) and missed abortion group (1200.86 ± 199.31pg/ml). In addition, patients in the ectopic group (1408.06 ± 219.02 pg/ml) had significant lower mean than patients in the missed abortion group (1848.24 ± 222.37 pg/ml).

Significant differences of follistatin mean ± SD between the three groups, p-value < 0.001. The control group had a significant lower mean of FST (2.71 ± 0.49 ng/ml) as compared to the ectopic group (4.64 ± 0.89 ng/ml) and missed abortion group (7.70 ± 1.64ng/ml). In addition, patients in the ectopic group had significant lower mean than patients in the missed abortion group.

Regarding ACV-A/ FST Ratio, control group had lower mean of ACV-A/ FST Ratio (291.93 ± 69.19) in compare to patients with missed abortion (251.14 ± 63.01). Patients with ectopic had higher mean (309.06 ± 55.75) in compare to patients with missed abortion (251.14 ± 63.01), with A significant difference of mean between the three groups, p-value 0.002, as presented in Table 1.

Table 1. Mean ± SD difference of ACV-A, FST and ACV-A/FST ratio between the groups.

	control	had ectopic pregnancy	had abortion	Total	p-value
ACV-A a, b, c	773.56 ± 130.26 (16.18)	1408.06 ± 219.02 (39.98)	1848.24 ± 222.37 (39.93)	1200.86 ± 199.31 (36.38)	< 0.001*
FST a, b, c	2.71 ± 0.49 (0.06)	4.64 ± 0.89 (0.16)	7.70 ± 1.64 (0.30)	4.44 ± 2.27 (0.20)	< 0.001*
ACV-A/ FST Ratio a, b, c	291.93 ± 69.19 (8.93)	309.06 ± 55.75 (10.17)	251.14 ± 63.01 (11.51)	286.01 ± 67.51 (6.16)	0.002*

a: control and ectopic preg. b: control and abortion c: ectopic preg. and missed abortion
***p-value is significant**

In patients with ectopic pregnancy, positive moderate correlation between ACV A and ratio of ACV/FST (r 0.59, p <0.001). A significant negative moderate correlation between FST and ratio of ACV/FST (r -0.57, p 0.001), as presented in Table 2.

Table 2. correlation between studied biomarkers in ectopic group.

		ACV-A (Activin A)	FST (Follistatin)	Human CGβ(B-HcG)	ratio
Age	Pearson Co.	0.18	0.08	-0.39*	0.05
	P-value	0.34	0.65	0.02	0.76
BMI	Pearson Co.	-0.25	-0.23	-0.07	-0.004
(kg/m)²	P-value	0.17	0.21	0.68	0.98
ACV-A	Pearson Co.	/	0.29	-0.11	0.59**
(Activin A)	P-value		0.10	0.56	<0.001
FST	Pearson Co.	0.29	/	-0.18	-0.57**
(Follistatin)	P-value	0.10		0.34	0.001
Human CGβ	Pearson Co.	-0.11	-0.18	/	0.04
(B-HcG)	P-value	0.56	0.34		0.80
ratio	Pearson Co.	0.59**	-0.57**	0.04	/
	P-value	<0.001	0.001	0.80	

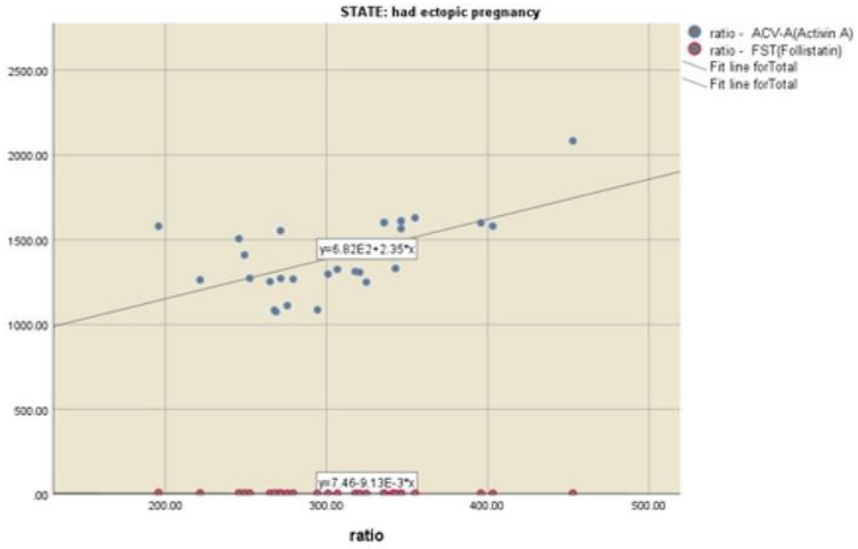


Figure 1. Correlation between ACV/FST ratio ACV and FST in ectopic group.

In the missed abortion group, Positive significant correlation between ACV-A and the ratio of ACV/FST (r 0.59, ps <0.001), significant negative very strong correlation between FST and the ratio of ACV/FST (r -0.661, p <0.001), Positive significant correlation between Beta-hCG and ratio of ACV/FST (r 0.59, p <0.001).

Significant negative strong correlation between Beta-hCG and FST (r -0.66, p <0.001), as presented in Table 3.

In order to differentiate ectopic pregnancy from other groups, Activin-A had AUC (0.688) with cut off value >1027, with 100% Sensitivity and 67% Specificity, while FST (Follistatin) had AUC(0.676) with cut off value >3.68, with 93% Sensitivity and 67% Specificity, and Human (Beta-hCG) had AUC(0.766) with cut off value >236, with 93% Sensitivity and 69% Specificity, as presented in Table 4.

Table 3. **Correlation between studied biomarkers in Missed abortion group.**

		ACV-A (Activin A)	FST (Follistatin)	Human CGβ (B-HcG)	ratio
Age	Pearson Co.	-0.11	0.19	-0.16	-0.11
	P-value	0.56	0.29	0.39	0.55
BMI	Pearson Co.	-0.10	-0.19	0.04	0.17
	P-value	0.60	0.30	0.83	0.35
ACV-A (Activin A)	Pearson Co.	/	-0.04	0.29	0.46**
	P-value		0.81	0.11	0.01
FST (Follistatin)	Pearson Co.	-0.04	/	-0.64**	-0.85**
	P-value	0.81		<0.001	<0.001
Human CGβ(B-HcG)	Pearson Co.	0.29	-0.64**	/	0.661**
	P-value	0.11	<0.001		<0.001
ratio	Pearson Co.	0.46**	-0.85**	0.661**	/
	P-value	0.01	<0.001	<0.001	

Table 4. **ROC test for ectopic pregnancy in biochemical marker in patients**.

Test Result Variable(s)	AUC	Cut off value	p-value	Sensitivity	Specificity
ACV-A (Activin A)	0.688	>1027	0.002	100%	67%
FST (Follistatin)	0.676	>3.68	0.004	93%	67%
Human CGβ (B-HcG)	0.766	>236	0.000	93%	69%

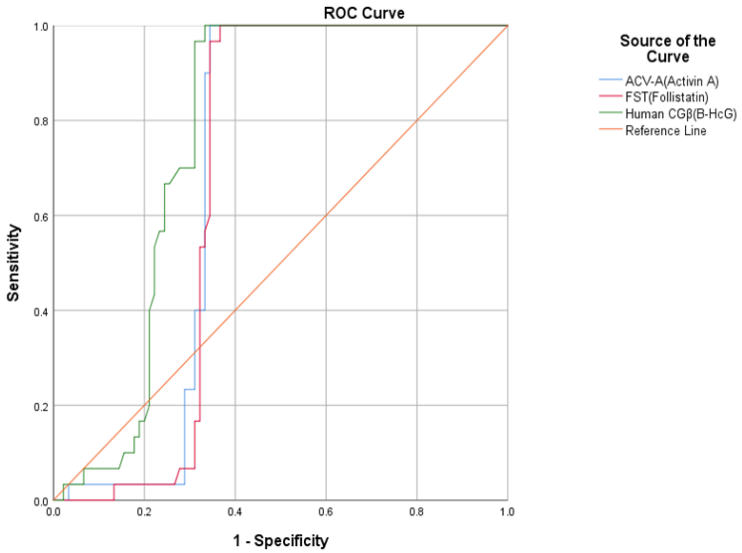


Figure 2. **ROC curve of ectopic pregnancy.**

In order to differentiate missed abortion patients from other patients, FST had the highest AUC of 0.98, a cutoff value >5.24, 96.7% sensitivity, and 94.4% specificity, as presented in Table 5.

Table 5. ROC test for missed abortion.

Test Result Variable(s)	Area	Cut off value	Sensitivity	Specificity	p-value
ACV-A (Activin A)	0.97	>1531	93%	92.2%	<0.001
FST(Follistatin)	0.98	>5.24	96.7%	94.4%	<0.001
Human CGβ(B-HcG)	0.88	>261	93.3%	77%	<0.001

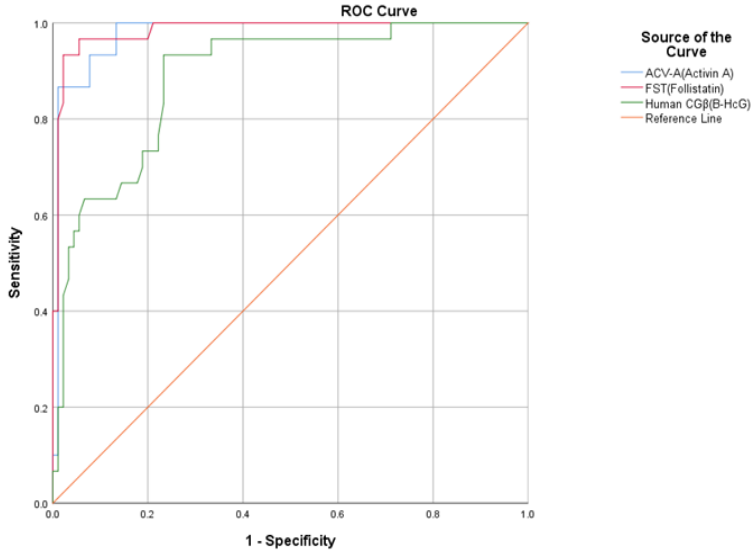


Figure 3. ROC curve for Missed abortion patients according The biochemical markers.

Discussion

The current study showed non-significant distinctions in mean values of age and BMI among the studied groups of patients and controls, which reflect their similarities among them (Table 1). The study was in agreement with Suliman AA, who found that age is not significantly associated with the risk of ectopic pregnancy **(21)** whereas the study of Jiang, et al. **(4)** found that being older did not increase the likelihood of a spontaneous abortion **(4)**. The study Salem **(22)** indicated that there is no statistical difference in age between the patients and the control and aborted cases **(22)**. The result of Zakira and Hardianto **(23)** found the women in the 25–29 age group had the lowest miscarriage risk (9.8%), followed by women in the 27–29 age group (9.5%) and women in the 45–plus age group (53.6%), according to the study **(23)**. The risk was 15.8% for mothers under the age of 20 years, Magnus MC **(24)**.

The present study showed no association between BMI groups and study groups, p≥0.5. These findings are in line with Ge, et al. **(25)**, who found no significant association was found between female BMI and the risk of ectopic pregnancy in cycles of spontaneously transferred embryos following controlled ovarian hyperstimulation (COH) following the correction of any confounding variables. On the other hand, Salem **(22)** found that there had been no significant variances in BMI between the study groups, and there were no substantial variances between BMI and the abortion occurrences Saleh and Galal **(26)** as well. According to several studies, there is not any evidence linking fat to abortion, and those who have a higher body mass index are at lower risk Candeloro, et al. **(27)**.

The findings indicated that there were significant differences in ACV-A mean between the three groups (p-value < 0.001). This study is in agreement with Al-Maini, et al. **(28)** who found that the serum levels of activin A, follistatin, and (activin A/FST) were significantly higher in a normal pregnancy compared to a failed pregnancy. In addition, the result of this study showed significant differences in the FST mean between the three groups (p-value < 0.001). This study is in line with Refaat and Bahathiq **(29)** who found that the level of follistatin in EP increased compared with IUP. Furthermore, ectopic pregnancy and spontaneous abortion (SAB) groups' serum levels of all activin and follistatin were significantly different from the IUP group's, suggesting that these proteins could serve as credible markers for the diagnosis of EP **(29)**.

These findings suggest that cytotrophoblasts secrete activin A. In tubal pregnancy, irregular decidualization

typically occurs with incorrectly implanted trophoblasts. However, on the other hand, elevated serum activin A may be found in ectopic pregnancies (Eps) if they are heterogeneous (one fetus inside the uterus).

Lu, et al. **(30)** showed that serum β-hCG is the sole indicator that is frequently and widely used in medical laboratories. Although β-hCG is not sensitive enough to diagnose EP, it can be useful in identifying patients who need to be closely monitored for early pregnancy failure. The expected Beta-hCG rise over 48 hours for viable intrauterine pregnancies (IUP) is at least 53%. However, for EPs, this method of diagnosis requires several days of follow-up, which increases the risk of tubal rupture **(30)**.

This study found that the activin A/FST ratio has a significant difference in mean between the three groups (p-value 0.002). This finding is in line with Al-Maini, et al. **(28)**, who found that the activin A/FS ratio was significantly higher in a normal pregnancy compared to a failed pregnancy. On the other hand, the study of Daponte, et al. **(31)** supports the thesis that a single measurement of activin A or FST at 6–8 weeks2of gestation makes it possible to distinguish between an unsuccessful pregnancy (MA or EP) and an IUP. More importantly, this study reveals the serum activin A's capability to distinguish between an EP and an MA. Their research revealed a relationship between EP and lower serum FS levels that was related to the low beta-hCG concentrations that were observed. While there have been several different studies investigating Warrick, et al. **(32)** the use of serum activin A as a biomarker for ectopic pregnancy, this is the first time that FS has been evaluated as such **(32)**.

On the other hand, the study of supports the idea that an IUP and a failed, pregnancy may be detected with just one measurement of activin A or FST at 6–8 weeks of gestations (MA or EP). More importantly, this study suggests serum activin A can distinguish between an EP and an MA. According to their study, there was a correlation between EP and lower serum FS levels, but not with the matching low beta-hCG concentrations. There have been several contradictory investigations into the use of serum activin A, even though this is the first time2that FS has been evaluated as a serum biomarker for ectopic pregnancy Warrick, et al. **(32)**. In normal pregnancy, because it is variable in response to changes in the decidualization process, activin A's expression is dynamic Johns, et al. **(33)**. Schneider-Kolsky, et al. **(34)** investigational findings from women with non-functioning ovaries have indicated that activin A originates in the fetus **(34)**.

However, in early pregnancy, Jones, et al. **(35)** found the cytotrophoblast is missing many activins, indicating that activins originating from the mother cause trophoblast invasion **(35)**. High activin A-levels were shown to increase 69-fold (with a broad range of values) during pregnancy, peaking at 45, 900±54, 000 p g/mL at weekss38–39 and about 700±200 pg/mL at days 6-7. Decidualization is helped and activated in vitro. The human endometrial stromal cell population generates cytokines Tierney and Giudice **(36)**. It is believed that this mechanism will be further impaired in ectopic pregnancies, and potentially even more so in unsuccessful pregnancies. When not viable trophoblasts are found, Florio, et al. **(37)** found activated protein A levels are decreased **(37)**, and Predicting miscarriage has been performed with both single and serial measurements Prakash, et al. **(38)**. Furthermore, Some EPs may have more active trophoblasts and behave more like IUPs, while others will be failing and behave more like failing MAs. It has been suggested that lower activin A levels in EP compared to those in other failed pregnancies may be due to the problems of the ectopic trophoblast successfully implanting, affecting the decidualization process Kirk, et al. **(39)**. If this is accurate, Warrick, et al. **(32)** it would explain why serum activin A levels varied among women with EPs in recent independent investigations, a fact that may have led to different findings regarding its discriminatory use in the differential diagnosis **(32)**.

Correlation among studied parameters

In the current study of patients with ectopic pregnancy, there is a significant negative weak correlation between age and Beta-hCG and a positive moderate correlation between ACV and the ratio of ACV to FST. There is a significant negative-moderate correlation between FST and the ratio of ACV to FST (Table 2, Figure 1).

Daponte, et al. **(31)** found Spearman's rank correlation coefficient (ρ) between Be-hCG and activin A and FS in IUP was 0.2140($P \geq$ 0.2840) 84 and 0.0320($P \geq 0.873$) and demonstrating that there is a weak correlation, the coefficient were 0.454 for activin Ai ($P \leq 0.0230$) and 0.4110for FS ($P \leq 0.041$), indicating a moderate correlation which is also statistically significant, For EP woman, there was non-significant correlation at 0.162t($P \geq 0.4830$) and −0.181t ($P \geq 0.431$) **(31)**.

In the abortion group, there is a positive moderate correlation between ACV and the ratio of ACV/FST, a significant negative very strong correlation between FST and the ratio of ACV/FST (person co. (-0.85**) , (p- value <0.001) , and a positive moderate correlation between B-hCG and the ratio of ACV/FST (Pearson co. (-0.661**) , (p- value <0.001) . There is a significant negative and strong correlation between B-hCG and FST (Table 3, Figure 2).

Saleh and Galal **(26)** stated that β-HCG is thought to be an additional cause of miscarriage. Additionally, a significant positive association has been seen between progesterone and β-HCG **(26)**. Muttukrishna, et al. **(40)** found that in women with a subsequent miscarriage, plasma activin A was positively correlated with inhibin A, progesterone and estradiol, HcG **(40)**.

Receiver Operation Characteristic (ROC) and Area Under Curve (AUC)

In order to differentiate ectopic pregnancy from other groups, human CGβ (B-hCG) had an AUC of 0.766 with a cut-off value >236, 93% sensitivity, and 69% specificity (Table 4, Figure 2). As the most commonly used serological indicator of EP, when it comes to the diagnosis of an early ectopic pregnancy, beta-hCG is crucial. In line with our experimental findings, low levels of beta-hCG may raise suspicions about EP, but beta-hCG by itself cannot prove or disprove EP **(41)**, whereas Ma, et al. **(42)** found the cutoff of Beta-hCG at 24,300 mIU/mL found a specificity of 77.78% (95% CI, 60.85–89.88) and sensitivity of 80.56% (95% CI, 63.98–91.81). On the other hand, the study of Ray, et al. **(43)** with ROC analysis yielded an area under the curve (AUC) score of 0.905 percentage points (95% confidence interval (CI): 0.814–0.996), it was possible to estimate, with a sensitivity of (84,9)%, a specificity of (83,3)%, a positive predicative value of (90,3)%, and a negative value of eighty-five percent, that levels of pre-treatment ≤ 4000 mIU/ml, had a higher probability of a favorable result under surgical treatment. There was a statistically significant finding for this ($p<0.05$). In another recent study, Sindiani, et al. **(44)** ROC analysis with a pretreatment The 76.19% sensitivity and 62.5% specificity of the beta-hCG cut-off value of 3924 IU/L were calculated, resulting in a 75% successful treatment percentage **(44)**.

Conclusion

- Serum Activin A and Follistatin levels can be used as indicators of Ectopic pregnancy and Missed Abortion.
- Obesity represented by BMI has no significant effect on patients with ectopic pregnancy or missed abortion.
- Serum CGβ (B-hCG) level at cutoff value of >236, ng/ml) may be a novel biomarker for assessment of women with ectopic pregnancy.
- Serum FST level at cut-off (>5.24) can be used as a novel biomarker of women with missed abortion.

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Authors' Contribution

Each author participated in data analysis, drafting, and revising of the manuscript, and consented to assume responsibility for all aspects of this project.

Conflict of Interest

The authors declared no conflicts of interest.

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