RESEARCH ARTICLE

Kisspeptin and activins in predicting early pregnancy loss

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ABSTRACT

Introduction: Measuring biomarkers like kisspeptin and activins might provide prognostic and diagnostic clues for early pregnancy loss and other diseases. Some of these biomarkers' increased or decreased values must be seriously considered, especially during pregnancy.

Objective: This study aims to identify the micro-organisms causing surgical site infection and their susceptibility patterns towards the common antibiotics in surgical words at Al-Nu'man Teaching Hospital.

Methods: A total of 90 women aged 18 and 40 years, less than 12 gestational weeks, were included in this case control study. Forty-six healthy pregnant women and 44 patients with early pregnancy loss (missed abortion) from the Gynecology and Obstetrics wards of the Al-Imamein A-lKadhimein Medical City between January 2022 and June 2022.

Results: The mean serum level of kisspeptin in early pregnancy loss is 2.4±0.88 ng/ml, much lower than that in healthy pregnant women (4.21±1.33 ng/ml) with a highly significant difference. Likewise, healthy women had a higher level of activin A (766.77±299.13 pg/ml) than women with early pregnancy loss (331.16±62.39 pg/ml) with a highly significant difference. In contrast, women with early pregnancy loss showed a higher level of activin AB than controls (378.82±98.72 pg/ml vs. 244.35±99.6 pg/ml) with a highly significant difference. There is a significant positive correlation between kisspeptin and the menstrual cycle duration (r=0.368, p= 0.018).

Conclusion: Kisspeptin, Activins A, and Activin AB may be utilized as promising prognostic biomarkers for women with early pregnancy loss.

Key words: Kisspeptin, activin A, Activin AB, miscarriage, biochemical pregnancies.

INTRODUCTION

The loss of a pregnancy before viability is often regarded as a miscarriage. Worldwide, there are 23 million miscarriages yearly, equating to 44 pregnancy losses per minute.[1] Approximately twenty-five per cent of pregnancies end in pregnancy loss, mostly in the first trimester below 13 weeks.[2]

It is still a complication that commonly occurs during pregnancy and affects women physically and mentally. Patients experience financial and mental pressures from recurrent clinical tests and therapies for threatening abortion. However, there is no consistent clinical indicator to expect it early.[3]

The current list of etiologies for miscarriage includes uterine anomalies, parental genetic abnormalities, and endocrine and immunologic disturbances. However, only 50% of all miscarriages can be adequately explained.[4]

Early pregnancies, or so-called "biochemical pregnancies," have a failure rate of up to 50%

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within four weeks after the last menstrual period (LMP). One in five pregnancy losses occurs within six weeks of gestation; by the second trimester, that number has dropped to one in forty.[7]

Earlier diagnosis, and quicker treatments, accurate and early prediction of pregnancy loss in the first trimester might enhance pregnancy outcomes. Obstetricians and gynaecologists should always be able to distinguish between viable and nonviable pregnancies using various diagnostic methods and provide patients with a broad scope of therapeutic options, including medicinal and surgical procedures.[8]

Kisspeptin was discovered as a suppressor of human malignant melanoma in 1996 in Hershey, Pennsylvania, USA-home of the renowned Hershey's kisses chocolates.[11] KISS1, as a receptor, gets its name from these sweets, with the "SS" standing for "suppressor sequence.[12] Kisspeptin neurons are negatively regulated by the sex hormones testosterone, progesterone, and estrogen. Inactivating mutations in kisspeptin or its receptor, in particular, cause hypogonadotropic hypogonadism in humans and mice. Furthermore, new data suggests that extra-hypothalamic kisspeptins may have a physiological function in influencing the activity of different brain systems,[13] and Kisspeptins and their receptor, KISS1R, can be expressed in various organs.[14] Numerous studies have previously been conducted on kisspeptin's function in hypogonadotropic hypogonadism, infertility, puberty abnormalities, and illnesses linked to insulin resistance, such as type 2 diabetes mellitus, polycystic ovarian syndrome, and obesity.[15]

Pregnancy causes a significant rise in kisspeptin levels through stimulation of the hypothalamus by the placental syncytiotrophoblasts to produce kisspeptin, which controls the invasion of placental syncytiotrophoblasts into uterine matrices. [14,15,16]

Activin is a molecule that may increase the release of follicle-stimulating hormone (FSH) from the pituitary gland, as opposed to inhibin, which got its name from its ability to inhibit FSH production selectively.[17] Activin isoforms, A, B, AB, C, and E subtypes, have been recommended as possible biomarkers to treat some disorders. Activins control various biological processes, including cellular proliferation, differentiation, and invasiveness, to improve the development and performance of numerous human tissues and organs.[18]

Activin-A is a glycoprotein dimeric of the super tumour growth factor-ß (TGF-ß) family; it was observed that serum Activn-A concentration was significantly lower in spontaneous abortion compared to normal intrauterine pregnancy, while serum activin B can differentiate between high-risk and low-risk pregnancy of unknown location (PUL), Activin A adds to the invasion and migration of trophoblast, and the raised activin A is found to be related with miscarriage in women.[19]

The current knowledge of activin A as a component of the reproductive system allows for its categorisation as a hormone, a growth factor, and a cytokine. Over more than 30 years of rigorous research, activin A was localised in male and female reproductive organs and several other organs and systems, including the brain, liver, lung, bone, and gut. Additionally, it contributes to embryonic differentiation, early pregnancy trophoblast uterine wall penetration, and fetal/newborn brain hypoxia protection.[17]

The objectives of this study were:

1. To compare the levels of Kisspeptin, Activin A, and Activin AB in pregnant women with pregnancy loss in the first trimester to those in women with normal pregnancy.
2. Measure the sensitivity and specificity of using Kisspeptin, Activin A, and Activin AB in predicting early pregnancy loss using the receiver operating curve.
3. To identify an association between the level of Kisspeptin, Activin A, and Activin AB with some demographic features, gynaecology and obstetric history, hormonal, and blood indices.

METHODS

Setting and study design: This is a case-control study conducted at the Gynecology and Obstetrics wards of the Al-Imamein Al-Kadhimein Medical City from January 2022 to June 2022.

Ethical consideration: The ethical research committee of the Al-Karkh Health Directorate approved the protocol for this study. We took the agreement of the administration of Al-Imamein Al-Kadhimein Medical City to perform the research and to use the records of the eligible patients. Informed consent was obtained from each participant after explaining the study's aims and procedure.

Definition of cases and control; inclusion and exclusion criteria:

Cases: We included 44 women aged 18 to 41 years who were diagnosed with missed abortions and were admitted to the gynaecology and obstetrics wards during the study period. For the sake of the inclusion of patients, missed abortion was defined as:

1. The absence of the fetal heartbeat in a pregnant woman below the 12th gestational week, whether or not it had previously been observed.
2. Having active vaginal bleeding at least six weeks of pregnancy with an undetected fetal heartbeat.

Women with chronic inflammatory illnesses, thyroid disorders, diabetes mellitus, hematologic disorders, thrombosis histories, systemic lupus erythematosus, numerous pregnancies, current infections, arthritis, uterine anomalies, molar pregnancy, and antiphospholipid syndrome were excluded from this study. Women with anembryonic pregnancy were also excluded from this study. To calculate the gestational age, we depended on the last menstrual cycle date supported by measuring the crown-rump length (CRL) via abdominal or transvaginal ultrasound examination. We depended only on the CRL measurement if the last menstrual period was uncertain.

Control: We included healthy women with normal, uncomplicated pregnancies under 12 weeks of gestation who visited the same department for any reason.

Sampling: The sample was selected conveniently

Data collection: We extracted demographic features from women in both groups: age, BMI, and smoking status, along with certain gynecological and obstetric parameters, such as age at menarche, regularity and duration of menstrual cycles, history of previous miscarriages, family history of miscarriages, gestational age, and number of previous pregnancies.

Up to 3 mL of blood was aspirated from women in the case and control groups using a 5 mL syringe from the capital vein into a plain test tube. The samples were left for 30 minutes at room temperature, then centrifuged at 3000 rpm for 15 minutes, and stored at -20 °C. We measured kisspeptin, activin A, activin AB, progesterone, and HCG levels using biochemical kits. Additionally, we measured white blood cells (WBC), red blood cells (RBC), neutrophils (N), lymphocytes (L), platelets (PLT), mean platelet volume (MPV), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), hematocrit (HCT), hemoglobin (HGB), mean cell volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelet distribution width (PDW), plateletcrit (PCT), and platelet large cell ratio (P-LCR).

We studied the association between demographic, hormonal, gynecological, obstetric, and hematological parameters and early pregnancy loss. Furthermore, we evaluated the ability of kisspeptin and activin A and AB to predict early pregnancy loss.

Statistical analysis: Statistical studies were conducted using SPSS software version 25.0. Continuous data were subjected to the Shapiro-Wilk test to determine their normality. Data with a normal distribution were shown as mean and standard deviation and

analysed using a Student t-test. Non-normally distributed data were provided as median and range and analysed using the Mann-Whitney U test. Categorical variables were reported as percentages and integers, and the Chi-square test was used to assess them. The predictive usefulness of haematological markers in predicting EPL was assessed using the receiver operating characteristic curve (ROC). A statistically significant difference existed when the p-value was equal to or less than 0.05.

RESULTS

Demographic characteristics of the study population: Women with early pregnancy loss (EPL) were slightly older than those without EPL, 28.7±6.83 years vs. 26.04±6.04 years. However, the difference was not significant. Likewise, the two groups had no significant differences in height, weight, or BM. There was no significant difference in smoking habits between the two groups, with a p=0.642, as indicated in Table 1.

Obstetric and gynecologic history of the study population: The obstetric and gynecologic histories of the tested groups are reported in Table 2. The mean age at menarche did not differ significantly between women with and without EPL, 12.96±1.35 years versus 13.05±1.28 years. However, the menstrual cycle was irregular in 27.27% of patients, while none of the women in the control group had such irregularity, with a highly significant difference. Moreover, the mean cycle duration in patients was 5.16±1.51 days, shorter than that of controls, 5.73±0.95 days, with a significant difference.

More than two-thirds of patients, 70.45%, had more than one miscarriage versus none of the control groups, with a highly significant difference. Additionally, family history of women with EPL was more common among patients than in controls, 38.64% vs. 4%, with a highly significant difference. Finally, 34.1% of patients had ≥4 parity compared with 2% of controls who had such parity with a highly significant difference, see Table 2.

Table 1 | Demographic data of the study population

Variables	EPL	Controls	p-value
Age, years	(n=44)	(n=46)	
Mean±SD	28.7±6.83	26.04±6.04	0.058
Range	18-40	18-40	
Body mass index, kg/m²			0.498
Mean±SD	26.42±3.63	25.8±3.81	
Range	19.98-35.38	19.7-33.2	
Smoking			0.642
Yes	2(4.55%)	2(4%)	
No	42(95.5%)	44(96%)	

Table 2 | Obstetrics and gynaecological history of the study population

Variable	EPL (n=44)	Controls (n=46)	p-value
Age at menarche, years			0.825
Mean±SD	12.96±1.35	13.05±1.28	
Range	11-17	11-17	
Cycle regularity			<0.001
Yes	32(77.73%)	46(100%)	
No	12(27.27%)	0(0%)	
Duration of the menstrual cycle, days			0.037
Mean±SD	5.16±1.51	5.73±0.95	
Range	3-9	3-7	
Gestational age, weeks			0.189
Mean±SD	10.75±3.71	12.07±5.51	
Range	5-20	4.27	
Number of miscarriages			<0.001
One	13(29.54%)	10(20%)	
More than one	31(70.45%)	36(80%)	
Family history of miscarriage			<0.001
Yes	17(38.64%)	2(4%)	
No	27(61.36%)	44(96%)	
Parity			<0.001
Nulliparous	6(13.64%)	12(24%)	
1-3	23(52.27%)	33(74%)	
≥4	15(34.1%)	1(2%)	

Table 3 | Hormonal data of the study population

Variable	EPL (n=44)	Controls (n=46)	p-value
Progesterone level, ng/mL			<0.001
Mean±SD	8.2±3.77	13.58±4.65	
Range	0.21-14.77	5.09-28.31	
hCG level, IU/L			0.233
Mean±SD	61.52±33.08	51.71±21.82	
Median	56.33	47.74	
Range	2.2-164.7	22.72-124.92	

hCG = human chorionic gonadotrophin

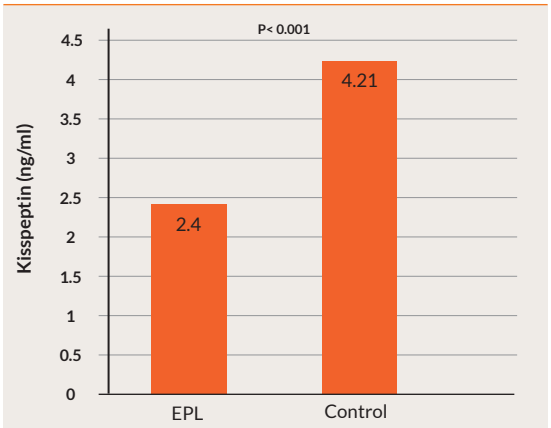

Figure 1 | Mean serum level of kisspeptin in women with EPL and healthy controls

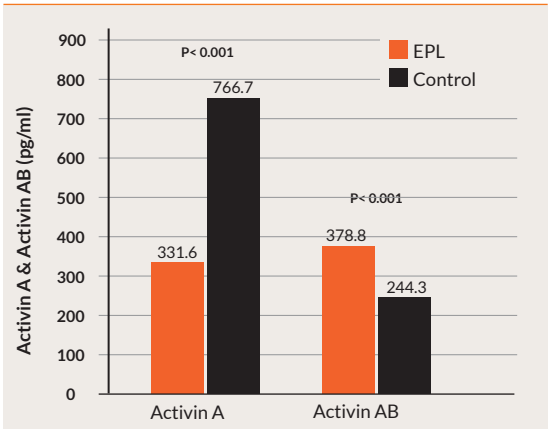

Figure 2 | Mean serum level of activin A and AB in women with EPL and healthy controls

Hormonal data of the study population: Women with EPL have a progesterone level of 8.2±3.77 ng/mL, much lower than the 13.5±4.57 ng/mL of the controls. Table 3 shows that the hCG levels in the two groups did not differ significantly, with a p value = 0.514.

Serum level of Kisspeptin and Activin AB: The mean serum level of kisspeptin in women with EPL was 2.4±0.88 ng/ml, which was much lower than that in healthy women, 4.21±1.33 ng/ml, with a highly significant difference as indicated in Figure 1. Likewise, healthy women had a higher level of activin A, 766.77±299.13 pg/ml, than women with EPL, 331.16±62.39 pg/ml, with a highly significant difference. In contrast, women with EPL showed a higher level of activin AB than controls, 378.82±98.72 pg/ml vs. 244.35±99.6 pg/ml, with a highly significant difference, see Figure 2.

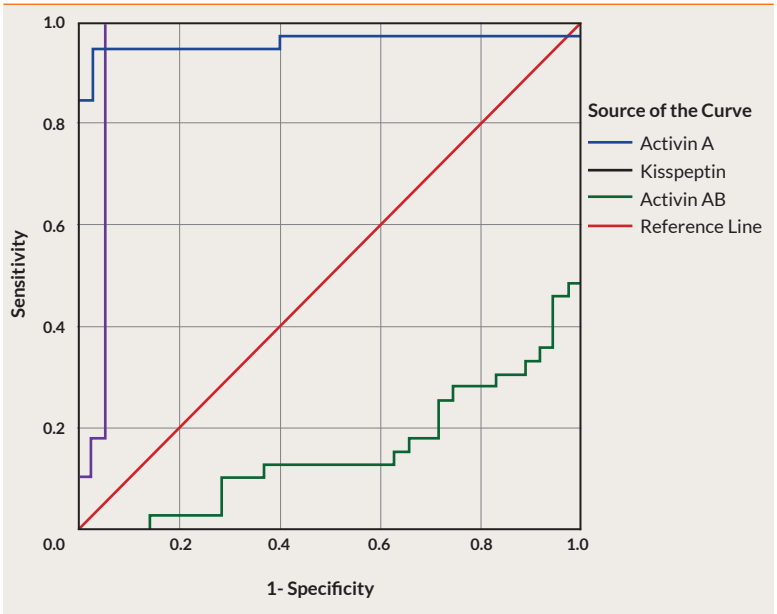

Figure 3 | Receiver operating characteristic curve for kisspeptin, activin A, and activin AB in predicting EPL

Predicting the value of Kisspeptin and Activin AB for EPL: For kisspeptin, the area under the curve (AUC) was 0.945, 95%CI= 0.883-1.0, p< 0.001. The sensitivity and specificity of the test at cut off value of kisspeptin= 2.74 ng/ml were 98% and 93%, respectively.

For activin A, the AUC was 0.965, 95%CI= 0.922-1.0, p< 0.001. The sensitivity and specificity of the test at cut off value of activin AB= 423.5 pg/ml were 96% and 95%, respectively. For activin AB, the AUC was 0.844, 95% CI= 0.755-0.933, p value < 0.001. The sensitivity and specificity of the test at the cut-off value of activin AB= 296.4 pg/ml were 83% and 82%, respectively (Figure 3).

Correlation of Kisspeptin, Activin AB, and Number of Miscarriage with other Variables in Patients: Generally, neither kisspeptin nor activin AB had a significant correlation with any of included variables. The only exception was the significant positive correlation between kisspeptin and the menstrual cycle duration (r=0.368, p= 0.018). On the other hand, the number of miscarriages had a significant positive correlation with age (r= 0.396, p value = 0.008) and the number of parity (r= 0.488, p value = 0.002), as shown in Table 4 and Figures

Table 4 | Pearson's correlation of kisspeptin, activin AB and number of miscarriages with other variables in patients

Variables	Kisspeptin		Activin A		Activin AB		No. of miscarriage	
	r	P-value	r	P-value	r	P-value	r	P-value
Age	0.262	0.098	0.091	0.573	-0.286	0.096	0.396	0.008
Gestational age	0.078	0.629	-0.217	0.173	-0.064	0.716	0.291	0.056
BMI	0.156	0.329	0.150	0.351	-0.262	0.128	0.092	0.553
Age at menarche	-0.019	0.922	0.033	0.868	0.047	0.822	-0.180	0.360
MC duration	0.368	0.018	0.253	0.111	0.025	0.886	0.062	0.692
Progesterone	-0.238	0.137	0.147	0.206	0.281	0.524	0.206	0.165
hCG	0.153	0.247	-0.054	0.964	0.120	0.923	-0.265	0.230
Parity	0.204	0.202	0.183	0.253	0.221	0.123	0.448	0.002
No. of miscarriage	-0.078	0.627	0.028	0.861	-0.045	0.876		

4 and 5.

Correlation of Kisspeptin, Activin AB, and Number of Miscarriage with Hematological parameters in Patients: The kisspeptin level has positive relationship with RDW-CV (r = 0.392, p = 0.012), WBC count (r = 0.325; p value = 0.04), and neutrophil count (r = 0.393, p value = 0.013). Moreover, activing A level show significant negative correlation with WBC count (r = -0.325; p value= 0.041). Activin AB had a negative significant correlation with each of HCT (r= -0.440, p value = 0.10) and Hb (r= 0.483, p value= 0.004) as shown in Table 5.

Association of Kisspeptin, Activin A, and Activin AB and Number of Miscarriage with other Variables in Patients: Regarding the association between kisspeptin, activin AB, and the number of miscarriages with smoking status, family history of miscarriage, and regularity of menstrual cycle, there was no significant association with any of these variables, see Table 6.

DISCUSSION

The present study revealed that the mean serum level of kisspeptin in women with EPL

Table 5 | Pearson's correlation of kisspeptin, activin AB and number of miscarriages with rheological parameters in patients with EPL

Variables	Kisspeptin		Activin A		Activin AB		No. of miscarriage	
	R	P-value	r	P-value	r	p-value	r	P-value
RBC	-0.140	0.389	0.015	0.925	-0.219	0.222	0.040	0.801
HCT	-0.261	0.103	-0.146	0.370	-0.440	0.010	0.017	0.916
Hb	-0.291	0.069	-0.143	0.378	-0.483	0.004	0.004	0.981
MCV	-0.150	0.361	-0.162	0.326	0.018	0.922	-0.058	0.714
MCH	-0.174	0.284	-0.182	0.261	-0.047	0.794	-0.039	0.806
MCHC	-0.178	0.271	-0.026	0.874	-0.128	0.477	-0.029	0.853
RDW-SD	0.300	0.06	-0.044	0.785	0.175	0.329	-0.017	0.916
RDW-CV	0.392	0.012	0.128	0.432	0.153	0..396	0.073	0.644
WBC	0.325	0.04	-0.325	0.041	-0.094	0.601	0.079	0.610
Neutrophil	0.393	0.013	-0.190	0.247	-0.095	0.613	0.110	0.487
Lymphocyte	-0.157	0.333	-0.307	0.054	-0.009	0.960	-0.081	0.606
Platelet	0.83	0.077	-0.054	0.743	0.075	0.677	-0.013	0.933
MPV	-0.053	0.751	0.013	0.935	-0.307	0.099	0.059	0.709
PDW	-0.022	0.892	0.043	0.796	-0.230	0.221	0.153	0.335
PLCR	-0.030	0.858	-0.017	0.916	-0.292	0.118	0.067	0.675

Table 6 | Association of Kisspeptin, activin A and activin AB and number of miscarriage with other variables in patients.

Variables	Kisspeptin	Activin A	Activin AB	No. miscarriage
Smoking				
No	2.41±0.9	331.1±62.6	397.4±100.14	1.11±1.65
Yes	2.121±0.32	332.5±82.16	358.8±87.45	------
p-value	0.654	0.975	0.841	------
Family history				
No	2.41±0.95	325.5±68.6	352.64±77.49	1.07±1.54
Yes	2.38±0.78	339.96±52.13	413.74±115.03	1.06±1.81
p-value	0.903	0.477	0.069	0.976
Regular MC				
No	2.55±1.43	323.1±60.44	379.56±81.02	0.75±0.86
Yes	2.34±0.58	334.1±62.39	370.23±106.3	1.19±1.83
p-value	0.514	0.622	0.455	0.435

was statistically significantly lower than that in healthy pregnant women, 2.4±0.88 ng/ml versus 4.21±1.33 ng/ml, with a p-value of 0.001.

In contrast, the hCG levels in the two groups did not differ significantly. This study's findings are supported by Sakr et al. estimation that the incidence of EPL is negatively correlated with serum kiss-I levels at the time of pregnancy diagnosis. They discovered that ß-hCG had a considerably lower prediction for EPL than decreased serum Kiss-I levels. To avoid the necessity for successive estimates, lower serum Kiss-I at the 12th gestational week or the development of EPL ensured the predictability of the result achieved at booking time. [20] Another study has found that Kisspeptin measurement is comparable to or more accurate than hCG in differentiating between miscarriage and viable intrauterine pregnancy after six weeks of gestation. Kisspeptin levels demonstrated a good diagnostic value when assessed after six weeks of pregnancy, with AUC of 0.902. (0.866, 0.937).[21]

Kisspeptin levels in the blood and placenta have been connected to pregnancy-related disorders. A pregnant woman's metabolism is impacted by kisspeptin. During the third trimester of a human pregnancy, its circulating levels increase over 10,000 times before rapidly returning to normal levels after birth, indicating that the placenta is one of the main sources of kisspeptin. Kisspeptin levels vary in pre-eclampsia, miscarriage, gestational diabetes, and obesity; hence, analysis of its plasma profile has been suggested as a predictor of gestational success.[22-25] Additionally, the failure of intrauterine trophoblast migration, a crucial procedure for the success of gestation and affected by kisspeptin expression, is linked to various gestational illnesses. [26] Yuksel et al. showed that it was possible to discriminate between a healthy pregnancy and an early-week miscarriage for the first time with a single serum kisspeptin level. Additionally, individuals with ectopic pregnancies had much higher serum kisspeptin levels than those with miscarriages.[27]

The current study showed that kisspeptin level has a positive relationship with red blood cell distribution width coefficient of variation (RDW-CV), r = 0.392 and p = 0.012, WBC count, r = 0.325 and p = 0.04, and neutrophil count, r = 0.393 and p = 0.013. Moreover, the activin AB level shows a significant negative correlation with WBC count (r = -0.325 and p = 0.041).

Raheem et al. obtained 100 blood samples from 100 women aged 20 to 40 who had had multiple abortions and 100 women who had not as a control group. Blood samples were examined for haemoglobin, total WBC, platelet count, RBC, progesterone and estrogen levels. He found lower HB, platelet counts and erythrocyte counts but higher WBC than

usual. In addition, the progesterone level was noticeably low, while the estrogen level was noticeably high. Abortion may happen from Abnormal haematological and hormonal levels and have various effects on pregnancy, including abortion.[28]

This study shows that healthy women had a higher level of activin A (766.77±299.13 pg/ml) than women with EPL (331.16±62.39 pg/ml), with a highly significant difference. In contrast, women with EPL showed a higher level of activin AB than controls (378.82±98.72 pg/ml vs. 244.35±99.6 pg/ml) with a highly significant difference. For activin A, the AUC was 0.965, 95% CI= 0.922-1.0, p < 0.001. The sensitivity and specificity of the test at the cut-off value of activin A= 423.5 pg/ml were 96% and 95%, respectively; for activin AB, the AUC was 0.844, 95%CI= 0.755-0.933, p< 0.001. The sensitivity and specificity of the test at a cut-off value of activin AB= 296.4 pg/ml were 83% and 82%, respectively. Activin A plays a biological role in establishing and maintaining normal pregnancy. Xu et al. similarly found that activin A in EPL women was significantly higher than in controls.[19]

Adu-Gyamfi and colleagues concluded that activins A, B, AB, C, and E and inhibins A and B are members of the transforming growth factor beta (TGF) superfamily that control various biological processes, such as cellular differentiation, proliferation, and invasiveness, to improve the synthesis and operation of several human tissues and organs. As therapeutic targets and biomarkers, several of these isoforms have been proposed for treating specific disorders, including physiological and pathological processes unique to the female reproductive system. [29]

Evan et al. created a sensitive and specific ELISA to quantify total (bound+free) activin AB, A and B in 1997. According to preliminary findings, the distribution of activin-AB isoform is more constrained than activin-A. The existence of activin-A and activin-AB in free form shows that both isoforms have a role in the maturation of the ovarian follicle.[30]

Ectopic pregnancy(EP) alters the serum concentrations of activin-A and activin-AB as noticed by Refaat et al., they found that both proteins are potentially sensitive and specific serum makers for the diagnosis of EP compared to ß-hCG. [31]

In a recent study, Calvert et al. found that pregnant and non-pregnant women had all hormones in their serum. Pregnant women had considerably greater levels of inhibin A, total inhibin, activin A, activin AB, follistatin, and GDF-15 than non-pregnant women. [32]

CONCLUSION

1. Kisspeptin may be useful as a marker for early diagnosis of early pregnancy loss.
2. Kisspeptin and activin A are specific and sensitive in differentiating between early pregnancy loss and normal pregnancy.
3. Activin AB is significantly higher in women with miscarriage and is reliable in diagnosing early pregnancy loss.

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Abbreviations list: Area under the curve (AUC), Crown-rump length (CRL), Early pregnancy loss (EPL), Ectopic pregnancy (EP), Enzyme-linked immunosorbent assay (ELISA), Follicle-stimulating hormone (FSH), Haematocrit (HCT), Haemoglobin (HGB), Human chorionic gonadotrophin (hCG), Last menstrual period (LMP), Lymphocytes (L), Mean cell volume (MCV), Mean corpuscular haemoglobin (MCH), Mean corpuscular haemoglobin concentration (MCHC), Mean platelet volume (MPV), Millilitre (mL), Neutrophil-lymphocyte ratio (NLR), Neutrophils (N), Platelet distribution width (PDW), Platelet large cell ratio (P-LCR), Plateletcrit (PCT), Platelet-lymphocyte ratio (PLR), Platelets (PLT), Red blood cells (RBC), Red cell distribution width (RDW), Statistical Package for the Social Sciences (SPSS), Transforming growth factor beta (TGF), United States of America (USA), White blood cells (WBC).

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