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Research Article

The Role of Kisspeptin in Discrimination Between Missed Miscarriage and Intrauterine Viable Pregnancy

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Abstract

Background: Missed miscarriage is a common complication, which affects 15% of pregnancies. The loss of a pregnancy is distressing for women and their partners. A biomarker for evaluation of the viability of gestation is kisspeptin because of the role of this marker is the regulation of trophoblast function and placentation. Kisspeptin plays a significant role in implantation and decidualization. ***Objective***: To evaluate the role of serum kisspeptin in discrimination between missed miscarriage and viable intrauterine pregnancy. ***Methods***: A case-control study was conducted in the Department of Obstetrics and Gynecology at Azadi Teaching Hospital, Kirkuk. It included 92 women with singleton pregnancies; they were divided into 2 groups: The case group included 45 pregnant women who presented with missed miscarriage, and the control group included 47 women with viable singleton pregnancy. Tests for kisspeptin level and β-hCG level were done for both groups. ***Results***: Kisspeptin and β-hCG values were significantly lower in miscarriage cases compared to the control group. The optimal kisspeptin level for the discrimination between miscarriage and viable intrauterine pregnancies was 53.3 ng/l. Hence, a kisspeptin level < 53.3 ng/l is a predictor for missed miscarriage. The optimal β-hCG level for the discrimination between miscarriage and viable intrauterine pregnancies was 8642.2 ng/l. The correlation between kisspeptin and β-hCG levels was a significant positive. ***Conclusions***: Kisspeptin and β-hCG levels are more sensitive and specific in predicting early missed miscarriage. They represent non-invasive, early, and excellent predictors of missed miscarriage, which can be used if confirmed by further studies.

Keywords: β-hCG, Kisspeptin, Miscarriage, Viable pregnancy.

دور كيسبيبتين في التمييز بين الإجهاض الفائت والحمل القابل للحياة داخل الرحم

الخلاصة

الخلفية: الإجهاض الفائت هو أحد المضاعفات الشائعة التي تؤثر على 15٪ من حالات الحمل. إن فقدان الحمل أمر محزن للنساء وشركائهن. المؤشر الحيوي لتقييم جدوى الحمل هو كيسبيبتين لأن دور هذه العلامة هو تنظيم وظيفة الأرومة الغاذية والمشيمة. يلعب كيسبيبتين دورا مهما في الزرع والتقطيع. **الهدف**: تقييم دور كيسبيبتين المصل في التمييز بين الإجهاض الفائت والحمل داخل الرحم القابل للحياة.**الطرائق**: أجريت دراسة حالة وشواهد في قسم أمراض النساء والتوليد في مستشفى آزادي التعليمي بكركوك. وشملت 92 امرأة مصابة بحمل فردي. تم تقسيمهم إلى مجموعتين: تضمنت مجموعة الحالة 45 امرأة حامل تعرضن للإجهاض الفائت، وشملت المجموعة الضابطة 47 امرأة مع حمل وحيد قابل للحياة. تم إجراء اختبارات لمستوى كيسبيبتين ومستوى β-hCG لكلا المجموعتين. **النتائج**: كانت قيم كيسبيبتين و β-hCG أقل بشكل ملحوظ في حالات الإجهاض مقارنة بالمجموعة الشاهدة. كان المستوى الأمثل للكيسبيبتين للتمييز بين الإجهاض والحمل داخل الرحم القابل للحياة 53.3 نانوغرام/لتر. ومن ثم، فإن مستوى كيسبيبتين < 53.3 نانوغرام/لتر هو مؤشر على الإجهاض الفائت. كان المستوى الأمثل β-hCG للتمييز بين الإجهاض والحمل داخل الرحم القابل للحياة 8642.2 نانوغرام/لتر. كانت العلاقة بين مستويات كيسبيبتين و β-hCG إيجابية ذات دلالة. **الاستنتاجات**: مستويات كيسبيبتين و β-hCG أكثر حساسية وتحديدا في التنبؤ بالإجهاض المبكر الفائت. وهي تمثل تنبؤات غير جراحية ومبكرة وممتازة للإجهاض الفائت، والتي يمكن استخدامها إذا تم تأكيدها من خلال مزيد من الدراسات.

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INTRODUCTION

A miscarriage is medically defined as the spontaneous loss of a pregnancy before the fetus reaches viability, which is legally considered to be before 24 weeks of gestation in the United Kingdom [1]. Ten to 20% of all clinically recognized pregnancies end in miscarriage [2]. Missed miscarriage occurs in the absence of symptoms or minimal symptoms, where the empty gestation sac or nonviable embryo is still visible within the uterus. It is observed in women who are asymptomatic or have vaginal bleeding [3]. There may be the presence of brownish vaginal discharge and subsidence of pregnancy symptoms such as regression of breast changes, cessation of uterine growth, etc. The fetal heart sounds may not be heard, and the immunological tests for pregnancy may become negative [4]. In recent years, the incidence of missed

miscarriage has increased, with its prevalence now exceeding 3% of all pregnancies [5]. Statistics indicate that missed miscarriages account for 17% to 22% of all types of miscarriages, possibly up to 40% of all conceptions [6]. While fetal chromosomal abnormalities are the leading cause of missed miscarriage, various other risk factors also contribute. These include personal factors, lifestyle, environmental factors, and miscellaneous factors [7]. Chromosomal abnormalities account for approximately 50% of spontaneous miscarriages, while the remaining 50% may be associated with environmental factors [8]. After the first trimester, the incidence of chromosomal abnormalities decreased [6]. Kisspeptin is a protein encoded by the *KISS1* gene in humans. Originally identified as a human metastasis suppressor gene, KISS1 has been found to inhibit the spread of melanoma and breast cancer [9]. In in vitro studies, kisspeptin has been shown to prevent the migration of trophoblasts by suppressing the activity of matrix metalloproteinases. Decreased levels of maternal serum kisspeptin in early pregnancy have been associated with the development of preeclampsia. Kisspeptin plays a crucial role in embryo implantation by interacting with cell adhesion molecules and promoting stromal decidualization through upregulating leukemia inhibitory factor (LIF) [10]. Kisspeptin levels are noticeably decreased by 60 to 79% in women who experience miscarriage compared to those with healthy pregnancies [11]. Additionally, it has been found that kisspeptin is higher in subfertile polycystic women [12]. *KISS-1* expression is lower in the trophoblast of pregnant women with recurrent spontaneous miscarriages compared to those undergoing elective termination. Moreover, kisspeptin is recognized for its high diagnostic accuracy in detecting miscarriage, and combining kisspeptin with β-hCG enhances diagnostic reliability at all gestations [13]. Kisspeptin levels are lower in cases of complete miscarriage compared to incomplete or missed miscarriage. Both kisspeptin and βeta-human Chorionic Gonadotrophin levels decline as miscarriage confirmation approaches [14]. This study evaluates the role of serum kisspeptin to discriminate between missed miscarriage and viable intrauterine pregnancy.

METHODS

Study design and patient selection

This was a case-control study conducted in the Department of Obstetrics and Gynecology at Azadi Teaching Hospital in Kirkuk over an eight-month period, from 1st of February till 1st of October 2023. Initially the study included 96 women aged between 18 and 40 years with singleton intrauterine pregnancy proved by a positive pregnancy test, serum β-hCG measurement, and ultrasound examination. Four participants showed invalid or missing kisspeptin results, so the total number of participants included in the analysis was 92. The study participants were categorized into two groups: Cases included 45 pregnant women who presented with missed miscarriage, and the control included 47 pregnant women with single viable pregnancies and no history of vaginal bleeding. Estimation of gestational age was done depending on the date of the last menstrual cycle and/or early ultrasound scan (US).

Inclusion criteria

Cases were selected from outpatient clinics or from patients admitted for termination of pregnancy, and they were diagnosed by US as a missed miscarriage in all cases below 12 weeks gestation; the diagnostic criteria by US are based on a mean sac diameter ≥ 25 mm, which is defined as an empty gestational sac or an embryo with crown rump length (CRL) ≥ 7 mm and no heartbeat. Selection of IUP cases: Pregnant women were included from those attending the hospital for their first routine booking visit at comparable gestational age with no history of vaginal bleeding, and the transvaginal ultrasound finding was intrauterine pregnancy six weeks and more with a positive fetal heart. Normally looking intrauterine gestational sac at 4-5 weeks who were followed for up to two weeks to confirm ongoing viable pregnancy, then followed up until confirmed that they were progressing to deliver a healthy term singleton baby.

Exclusion criteria

The cases that are excluded from the study include maternal age < 18 and > 40, gestational age more than 12 weeks, molar pregnancy, ectopic pregnancy, multiple pregnancy, maternal medical diseases (DM, HT, liver disease, and others), women on exogenous progesterone, women conceived after ovarian stimulation or by in vitro fertilization (IVF), chronic use of drugs such as anti-inflammatories, anticoagulants, and antioxidants, smokers, and immunized Rh-negative women.

Outcome measurements

A questionnaire was designed by the researcher after reviewing the literature and was applied to all enrolled pregnant women. It was then reviewed by the supervisor. Detailed history was taken, including age of participants, blood group and Rh, obstetrical and gynecological history, previous gynecological surgeries, chronic medical diseases, and drug history (e.g., heparin or progesterone). All participants were subjected to complete physical examinations, including general examinations, vital signs, and abdominal examinations. Body mass index (BMI) was calculated for all the subjects. BMI = Weight (kg)/Square height (m^2) [15]. Pelvic examination for all patients in both groups for evaluation of the uterine size and cervical

dilatation. In addition to routine investigations, which include CBC, blood group and Rh, blood sugar, etc., we evaluated kisspeptin and β-hCG levels in the serum for both groups.

Ethical consideration

Prior to the collection of data, verbal permission was obtained from each participant, and information was anonymous. Their names were removed and replaced by identification codes. Administrative approvals were granted from the Council of Iraqi Board of Medical Specialization and Approval of the Department of Obstetrics and Gynecology at College of Medicine, University of Kirkuk (Certificate No. 51 in 2/1/2024).

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS) version 26. The results are presented as means, standard deviations, and ranges, while categorical data are presented as frequencies and percentages. The significance of the difference of different means was tested using Student's t-test for the difference between two independent means. Receiver operating characteristic (ROC) was used for evaluation of the ability of kisspeptin and β-hCG levels for prediction of miscarriage. The optimal cutoff values were determined using the Youden index. Specificity, sensitivity, negative predictive value (NPV), and positive predictive value (PPV) were calculated. The diagnostic ability of kisspeptin and β-hCG levels was also assessed based on the area under the curve (AUC). The correlation coefficient value (R) is either positive (direct correlation) or negative (inverse correlation). A value <0.3 represents no correlation, 0.3 - < 0.5 represents weak correlation, 0.5 - < 0.7 represents moderate strength, and > 0.7 represents strong correlation. A level of *p*-value less than 0.05 was considered significant.

RESULTS

The mean age of the case group was 30.15±5.28 years versus 29.36±5.31 for the control group. The highest proportion of participant women were 30-34 years, 42.2% in the case group and 36.2% in the control group (Figure 1).

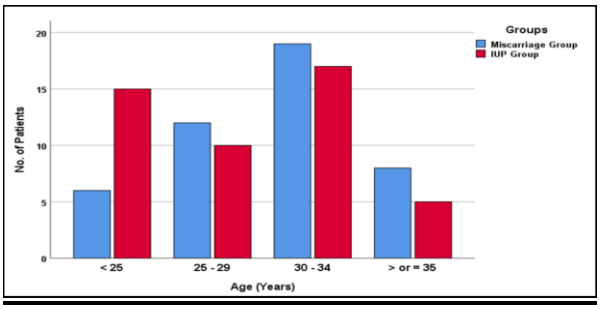

Figure 1: Age distribution of the study groups.

The calculated BMI of the case group had a mean of 26.37±5.31 kg/cm^2 versus 25.27±5.02 kg/m^2 for the control group. Concerning parity, 46.7% of the case group had a parity history of 1.0-4.0, while 42.6% of the control group were nulliparous. Previous miscarriage was reported by 53.6% in the case group; in the control group, 10 patients had a history of one miscarriage (Table 1).

Table 1: Categorization of study groups based on specific clinical characteristics

Patients characteristics	Study Groups		Total (n=92)
	Cases (n= 45)	Controls (n= 47)	
BMI (kg/m^2)			
Normal	7(15.6)	14(29.8)	21(22.8)
Overweight	34(75.6)	33(70.2)	67(72.8)
Obese	4(8.8)	0(0)	4(4.4)
Parity			
0	10(22.2)	20(42.6)	30(32.6)
1 – 4	21(46.7)	19 (40.4)	40(43.5)
≥ 5	14(31.1)	8(17.0)	22(23.9)
Gestational age (week)			
5-8	30(66.7)	22(46.8)	52(56.5)
9-12	15(33.3)	25(53.2)	40(43.5)
History of subfertility			
Yes	4(8.8)	3(6.4)	7(7.6)
No	4(91.2)	44(93.6)	85(92.4)
Previous miscarriage			
Yes	16(35.6)	10(21.3)	26(28.3)
No	29(64.4)	37(78.7)	66(71.7)
Number of miscarriages	n= 16	n= 10	
1	8(50.0)	10(100.0)	18(69.2)
2	2(12.5)	0(0.0)	2(7.7)
≥ 3	6(38.5)	0(0.0)	6(23.1)

Values were expressed as frequency and percentage.

When compared to the control, the kisspeptin levels were significantly lower in the case (49.37 *vs*. 58.69 ng/l, p = 0.001) (Figure 2). Receiver operating characteristic (ROC) curve analysis showed that the optimal kisspeptin level for the discrimination between missed miscarriage and viable intrauterine pregnancies

was 53.3 ng/l. Therefore, a kisspeptin level of less than 53.3 ng/l is a predictor of missed miscarriage, as evidenced by a large and significant area under the curve (AUC = 87.6%), which indicates a strong association between lower kisspeptin levels and miscarriage.

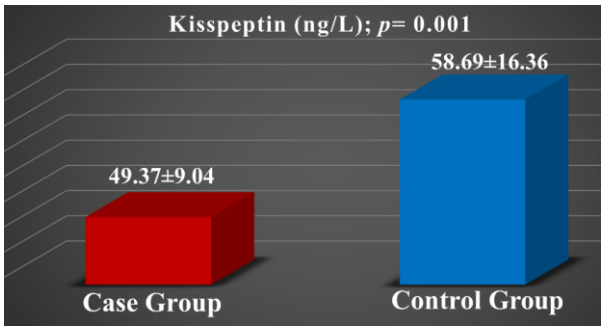

Figure 2: Distribution of the study groups according to kisspeptin levels.

This cutoff value achieved a sensitivity of 95.1%, specificity of 77.5%, and an accuracy of 86.3%. The positive predictive value (PPV) of kisspeptin was 80.9%, and the negative predictive value (NPV) was 93.9% (Figure 3).

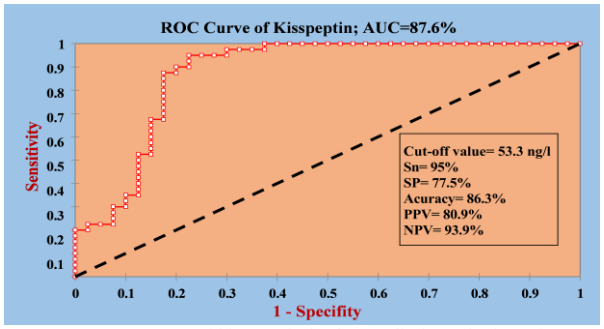

Figure 3: ROC curve of kisspeptin in the prediction of miscarriage.

This study found a statistically significant difference in the mean β-hCG levels between the studied groups. Women in the case group had significantly lower β-hCG levels than women in the control group (7056.4 *vs*. 13058 ng/l, $p = 0.038$) (Figure 4).

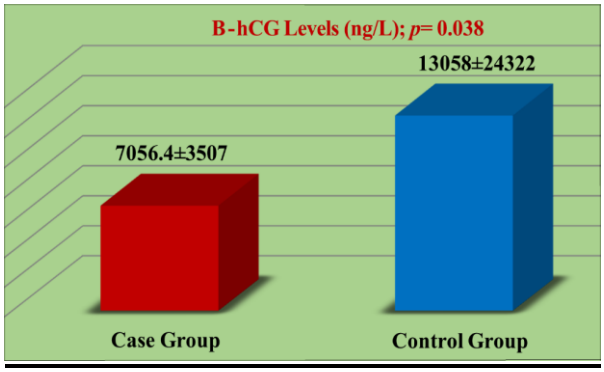

Figure 4: Distribution of the study groups according to β-hCG levels.

ROC curve analysis for β-hCG levels as predictors of missed miscarriage. The optimal β-hCG level for the discrimination between missed miscarriage and viable intrauterine pregnancies was 8642.2 ng/l. Hence, a β-hCG level < 8642.2 ng/l is a predictor for missed miscarriage, as a large significant area under the curve (AUC = 95.1%) indicates a significant association between the lower β-hCG levels and miscarriage. This cut-off value obtained a sensitivity of 86.7% and specificity of 97%, with an accuracy of 91.2%. PPV was 96.8% and NPV was 87.8% (Figure 5).

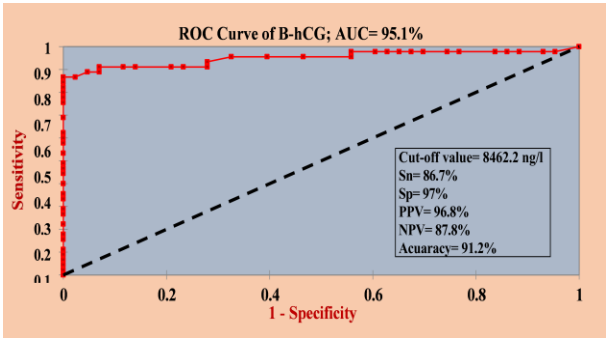

Figure 5: ROC curve of β-hCG in prediction of miscarriage.

In the Pearson correlation analysis, there was a significant positive correlation between kisspeptin and β-hCG levels (R = 0.341, $p = 0.001$) (Figure 6).

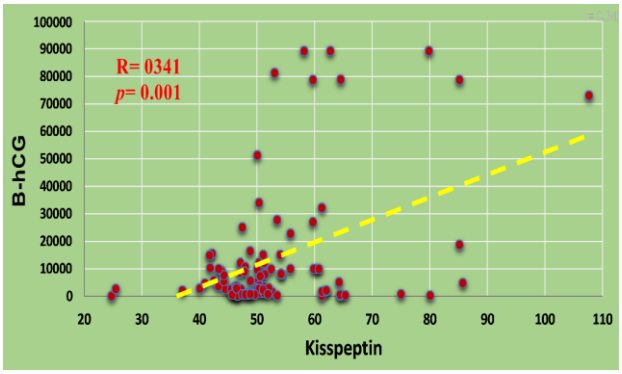

Figure 6: Correlation between kisspeptin (ng/L) and β-hCG (ng/L) levels.

DISCUSSION

Miscarriage is defined as loss of a pregnancy before 12 weeks, known as early miscarriage, or between 12 and 24 weeks of gestation, referred to as late miscarriage [16]. In clinical practice, ultrasound is commonly used to assess the viability of embryos [17]. However, while ultrasound can confirm viability, it cannot determine the prognosis of the pregnancy. Various hormonal markers have been studied to aid in the prediction of pregnancy outcome, including β-human chorionic gonadotropin, progesterone, activin A, activin B, kisspeptin, CA-125, and pregnancy-associated plasma protein A (PAPP-A) [18]. Among these, kisspeptin is considered a biomarker for determining pregnancy viability; this may be because of its potential role in regulating trophoblast activity and placental function [19]. Kisspeptin levels increase with gestational age,

suggesting that kisspeptin can be a marker of placental dysfunction [20]. In the present work, the mean and standard deviation of age in the case group was 30.15±5.28 versus 29.36±5.31 years in the control group. The calculated BMI of the case group had a mean of 26.37±5.31 kg/m^2. In the Marwah *et al*. study, a different result was observed; they found that the mean age was 23.7±3.9 years in the case group. The mean BMI of patients was 21.713±2.2017 kg/m^2 [21]. In the Adnan *et al*. study, they found that 21% of women are 15-25 years old, 52.3% are between 26-35 years old, and 25.7% are between 36-45 years old [22], while in the Sullivan *et al*. study, the mean maternal age is 30.9±6.4 years [13]. Differences observed among the above studies can be attributed to the sample size enrolled in each study and differences in methodology and specificity of the procedure, and the test combination and timing of screening during pregnancy also contributed to differences in results. Concerning parity in this study, 46.7% of patients in the case group had a parity of 1-4. Also, 8.8% of the case group and 6.4% of the control group had a history of subfertility. Previous miscarriage was reported in 35.6% of the case group; of them, 50% of patients had one miscarriage. While in the Marwah *et al*. study, most patients were primigravida (72%), and among the remaining, 36% of women had previous miscarriages [21]. In a study by Adnan *et al*., 14.8% were primiparous, 86.6% were multiparous, and they revealed that 67% of pregnancies were ≤ 8.0 weeks of gestation, whereas 33% of others were between 8 and 12 weeks [22]. In the present study, kisspeptin levels were decreased significantly in cases compared with the healthy pregnant control (p = 0.001). This result aligns with the Hu *et al*. study, which analyzed kisspeptin level at the time of pregnancy testing and found it was significantly lower in the miscarriage group than in pregnancy groups [10]. Another similar finding was observed in the Sullivan *et al.* study, in which they observed that serum kisspeptin levels are significantly higher in those with normal intrauterine pregnancy in comparison to those with confirmed miscarriage (p < 0.0001) [13]. In the Abbara *et al*. study, which included healthy controlled pregnancies, the kisspeptin levels in plasma increased with advancing gestation during the first 14 weeks of pregnancy, and its level is reduced significantly in pregnant women with pregnancies that were complicated by miscarriage at all gestational ages (p < 0.05) [11]. In the present study, the optimal kisspeptin level for the discrimination between miscarriage and viable intrauterine pregnancies was 53.3 ng/l. So, a kisspeptin level < 53.3 ng/l is a predictor for miscarriage, with sensitivity and specificity of 95% and 77.5%, respectively, with an accuracy of 86.3%. The positive predictive value (PPV) and negative predictive value (NPV) of kisspeptin were 80.9% and 93.9%, respectively. In the same accordance, receiver operator characteristic curve analysis applied in a study conducted by Sullivan and other co-authors demonstrates an excellent accuracy of the kisspeptin assay in discriminating miscarriage from intrauterine pregnancy at the time of diagnosis (AUC 0.95; 95% CI 0.89-1.0]) [13]. In a study conducted by Jayasena *et al*., ROC curve analysis identified that the threshold of kisspeptin of 1630 pmol/L with 86% sensitivity and 70% specificity for identification of miscarriage. Additionally, a level of 1463 pmol/L showed 80% sensitivity and 75% specificity [2]. Kisspeptin expression is abundant in the syncytiotrophoblast during pregnancy. Increasing evidence suggests its crucial role in the regulation of early pregnancy events such as embryo implantation. Successful placentation and continuation of normal pregnancy require invasion of extravillous trophoblast, a process that shares striking similarities with the invasive behavior of cancer cells [23]. 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 control group (p = 0.038). An agreement observed in a study conducted by Mansy and colleagues [24], the Hu *et al*. study [10], and Sullivan and colleagues [13]. Furthermore, the Abbara *et al*. study observed that plasma β-hCG levels peaked at 8 weeks of pregnancy and were significantly lower in pregnancies that ended in miscarriage across most gestational ages [11]. In this study, ROC curve analysis was used to evaluate β-hCG levels as predictors of miscarriage. The optimal β-hCG level for distinguishing between miscarriage and viable intrauterine pregnancies was 8642.2 ng/l, yielding a sensitivity of 86.7% and specificity of 97%, with an accuracy of 91.2%. PPV was 96.8% and NPV was 87.8%. In another study, Mansy *et al*. reported a different finding, with their study identifying a β-hCG cut-off value of 2476 ng/l, which had a sensitivity of 79% and a specificity of 85.17% for predicting miscarriage [24]. Differences observed among the above studies in sensitivity and specificity of β-hCG can be attributed to those differences in methodology, procedures, and timing of sample collection. In addition, the high or low cut-off level values in different studies may be due to therapeutic application of progesterone and to the different gestational age or the duration of miscarriage. In the Abbara *et al*. study, ROC analysis was done to identify the ability of plasma levels to differentiate between healthy pregnancies and those affected by miscarriage. The accuracy of ROC was 0.859 (95% CI: 0.82–0.899) for β-hCG [11]. Human chorionic gonadotropin (β-hCG) is a glycoprotein composed of α- and β-subunits, secreted from syncytiotrophoblasts of the placenta, and peaks at 10 weeks of gestation. Human chorionic gonadotropin is the most extensively studied biomarker of early pregnancy outcomes. When it is used as a single value, it is considered to be non-diagnostic;

however, serial assessment of serum hCG levels is useful in the identification of pregnant women who need closer surveillance for early pregnancy failure. hCG has been utilized alone or in combination with progesterone, estradiol, testosterone, CA125, human placental lactogen (hPL), and ultrasonography in several studies to evaluate the prognosis of threatened abortion [25]. In the Pearson correlation analysis used in this study, there was a weak but significant positive correlation between kisspeptin and β-hCG levels (R = 0.341, p = 0.001). This finding agreed with that published in the Hu *et al*. study, in which they reported that serum kisspeptin level had a moderate positive relationship with β-hCG (R = 0.61; $p < 0.01$) [10]. In addition, Sullivan *et al*. conducted a study in which serum kisspeptin levels were measured using ELISA in pregnant women who presented with vaginal bleeding, cramping, or both at the emergency department. They found a significant positive correlation between kisspeptin and β-hCG levels in women who had a spontaneous miscarriage (p = 0.032) [13]. Also, there is a positive correlation between kisspeptin and β-hCG observed in the Jayasena *et al*. study [2]. The high diagnostic performance of kisspeptin for detecting miscarriage remains evident even in the later weeks of the first trimester (> 8 weeks of gestation). Therefore, combining kisspeptin with β-hCG at all gestational stages can significantly enhance diagnostic accuracy, with a reported confidence interval of 95% (CI: 0.89-0.95). Both kisspeptin and β-hCG levels decline as miscarriage confirmation approaches, making their repeated assessment every 1–2 weeks a useful strategy for further stratifying miscarriage risk. However, since kisspeptin expression is relatively low before 6 weeks of gestation, evaluating β-hCG levels may be more beneficial in the very early stages of pregnancy [26].

Conclusions

Kisspeptin is more sensitive than β-hCG in the prediction of missed miscarriage, while β-hCG is more specific. There was a significant positive correlation between kisspeptin and β-hCG in the prediction of missed miscarriage. Kisspeptin and β-hCG represented non-invasive, early, fast, and excellent predictors of missed miscarriage, which can be used if confirmed by further studies.

Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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