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Original Research Article

Association of Serum Kisspeptin with Miscarriage among Pregnant Women Attending an Antenatal Clinic at SMS Medical College, Jaipur

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Abstract

Background: Miscarriage is a common complication of early pregnancy, and early prediction remains a clinical challenge. Kisspeptin, a placental peptide hormone, has emerged as a potential biomarker for assessing pregnancy viability.

Aim and Objective: To evaluate the association of serum kisspeptin levels with miscarriage and to assess its predictive value in comparison with serum human chorionic gonadotropin (hCG).

Materials and Methods: This descriptive longitudinal observational study was conducted on 178 asymptomatic pregnant women (6–16 weeks gestation) attending the antenatal clinic at SMS Medical College, Jaipur. Participants were followed up until 20 weeks and categorized into miscarriage (n=13) and non-miscarriage (n=165) groups. Serum kisspeptin levels were measured using ELISA, and hCG was estimated by chemiluminescent immunoassay. Statistical analysis included t-test, chi-square test and ROC curve analysis.

Results: Serum kisspeptin levels were significantly lower in women with miscarriage compared to those with viable pregnancies (0.73 ± 0.28 vs 2.96 ± 1.84 ng/mL; $p=0.001$). Kisspeptin showed a significant positive correlation with gestational age ($r=0.389$, $p<0.001$). ROC analysis demonstrated excellent diagnostic performance for kisspeptin (AUC=0.980) with 92.3% sensitivity and 97.6% specificity at a cut-off ≤0.9735 ng/mL. In comparison, hCG showed lower diagnostic accuracy (AUC=0.792).

Conclusion: Serum kisspeptin is a highly sensitive and specific biomarker for early prediction of miscarriage and performs better than hCG. Its use in early antenatal screening may improve identification of high-risk pregnancies.

Keywords Kisspeptin; Miscarriage; Early pregnancy; Biomarker; Human chorionic gonadotropin (hCG); Pregnancy outcome; Placental function; Antenatal screening; ELISA; ROC analysis.

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Introduction

Miscarriage, defined as the spontaneous loss of pregnancy before 20 weeks of gestation, is one of the most common complications of early pregnancy, affecting approximately 10–20% of clinically recognized pregnancies worldwide [1]. The majority of miscarriages occur during the first trimester and are often attributed to chromosomal abnormalities, endocrine dysfunction, immune disturbances, and placental insufficiency [2,3].

Despite advances in obstetric care, early prediction of miscarriage remains a clinical challenge. In recent years, there has been increasing interest in identifying reliable biochemical markers that can predict pregnancy viability at an early stage. Among these, kisspeptin, a peptide hormone encoded by the *KISS1* gene, has emerged as a promising biomarker. Kisspeptin plays a crucial role in the regulation of the hypothalamic–pituitary–gonadal (HPG) axis and is essential for reproductive function [4]. It is highly expressed in placental trophoblastic tissue, where it is believed to regulate trophoblast invasion and placental development [5]. Serum kisspeptin levels rise significantly during normal pregnancy, particularly in the first trimester, reflecting placental activity [6].

Studies have demonstrated that lower levels of circulating kisspeptin are associated with impaired placentation and adverse pregnancy outcomes, including miscarriage [7]. Therefore, measurement of serum kisspeptin may serve as a sensitive indicator of early placental function. Human

chorionic gonadotropin (hCG), another well-established marker of early pregnancy, is widely used in clinical practice to assess pregnancy viability. However, hCG levels can show considerable variability and may not always reliably predict miscarriage when used alone [8].

Combining newer biomarkers such as kisspeptin with traditional markers like hCG may improve diagnostic accuracy. Previous studies, including those by Jayasena et al., have reported significantly reduced serum kisspeptin levels in women who subsequently experienced miscarriage compared to those with viable pregnancies [9]. Furthermore, kisspeptin has demonstrated superior diagnostic performance in predicting miscarriage, with higher sensitivity and specificity compared to conventional markers [10].

Given the limited data available from the Indian population, particularly in Rajasthan, there is a need to evaluate the role of serum kisspeptin in predicting miscarriage in this demographic setting. This study was therefore undertaken to assess the association of serum kisspeptin levels with miscarriage among pregnant women attending the antenatal clinic at SMS Medical College, Jaipur, and to compare its predictive value with serum hCG levels.

Materials and Methods

This descriptive, longitudinal observational study was conducted in the Department of Biochemistry in collaboration with the Department of Obstetrics and Gynaecology at S.M.S. Medical College and its attached hospitals, Jaipur.

The study protocol was approved by the Institutional Clinical Trial and Screening Committee (CTSC) and the Ethics Committee. Written informed consent was obtained from all participants prior to inclusion in the study. A total of 178 asymptomatic pregnant women with gestational age between 6 and 16 weeks, attending routine antenatal booking visits between June 2017 to November 2018, were recruited from the antenatal clinic. Participants were followed up until 20 weeks of gestation.

Participants were divided into two groups based on pregnancy outcome:

- **Group A:** Women who experienced miscarriage
- **Group B:** Women without miscarriage

Inclusion Criteria

- Asymptomatic pregnant women
- Gestational age between 6 to 16 weeks
- Attending routine antenatal booking visit

Exclusion Criteria

- Women with renal failure
- Emergency admissions
- Suspected miscarriage at presentation
- Known medical disorders such as thyroid disease, diabetes mellitus, and hepatic disease

Sample Collection and Processing: Venous blood samples were collected from the antecubital vein using aseptic precautions. Blood was collected in plain and EDTA vials. Serum was separated by centrifugation at 1300–1800 rpm for 10 minutes. Routine biochemical investigations were performed on the same day. Serum samples for kisspeptin estimation were stored at −20°C until analysis. Serum kisspeptin levels were measured using a commercially available ELISA kit based on a sandwich enzyme-linked immunosorbent assay technique. Serum human chorionic gonadotropin (hCG) levels were measured using a chemiluminescent immunometric assay on the Immulite 2000 system. Data were analyzed using SPSS software version 23.0 (SPSS Inc., Chicago, IL, USA).

Results and Observations

Table 1: Demographic characteristics of study participants and comparison between groups (N = 178)

Variables	Overall (N=178) Mean ± SD	Median	Range	P25	P50	P75	Group A (Miscarriage) (n=13) Mean ± SD	Group B (No Miscarriage) (n=165) Mean ± SD	P value
Maternal Age (years)	24.90 ± 3.70	25.00	19–40	22.00	25.00	27.00	23.46 ± 3.73	25.02 ± 3.68	0.138
Gestational Age (weeks)	10.23 ± 2.70	10.07	6–16	8.11	10.07	12.71	9.82 ± 3.07	10.27 ± 2.67	0.568

Table 1 presents the comparative study of demographic variable in group A and group B. The mean age of women with miscarriage was (23.46±3.73) years in that of women without miscarriage (25.02±3.68) years respectively. The mean GA (weeks) was 9.82±3.07 v/s 10.27±2.67 in women with miscarriage and women without miscarriage respectively, was statistically not significant ($p > 0.05$).

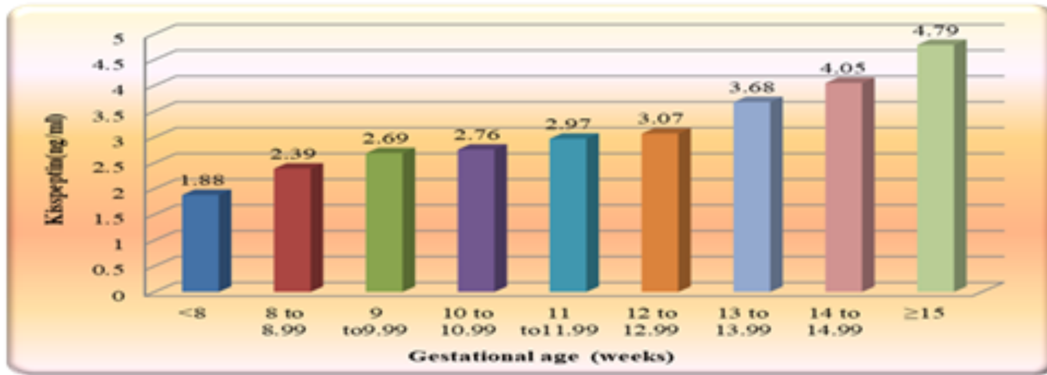

Figure 1: Showing serum kisspeptin level was continuously increases with gestational weeks (<8week kisspeptin level was1.88±1.14 ng/ml and in >15week kisspeptin level was 4.79±1.60 ng/ml)

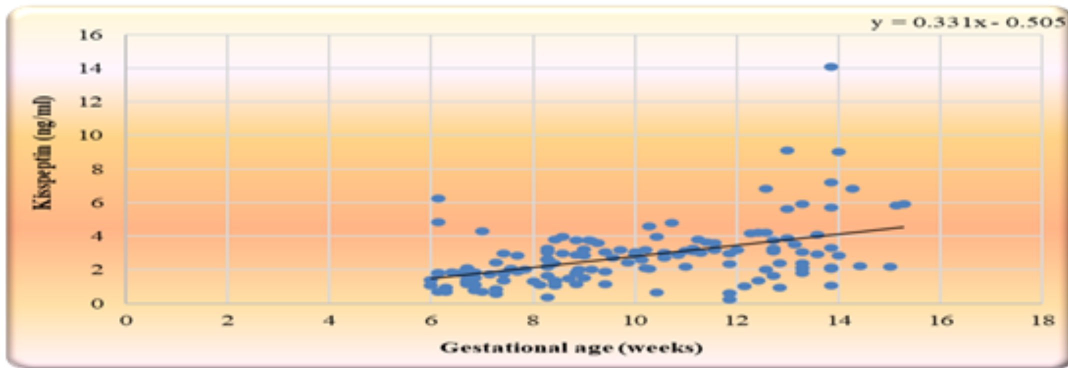

Figure 2: Correlation of serum kisspeptin levels with gestational age

A significant positive correlation existed between the kisspeptin with gestational age in pregnant women (r= 0.389; P=<0.000). The relationship between the variables in the study group were considered by using pearson's correlation coefficient (r^2 = 0.151).

Table 2: Comparative analysis of serum kisspeptin and hCG levels among study groups (N = 178)

Parameter	**Measure**	**Women with Miscarriage (Group A, n=13)**	**Women without Miscarriage (Group B, n=165)**	**P value**
hCG (mIU/ml)	Median (IQR)	45280.0 (27670.5–45280.0)	89372.0 (58104.5–136087.0)	<0.001
	Mean ± SD	48725.31 ± 21933.20	97137.53 ± 53745.46	0.002
hCG MoM	Mean ± SD	0.57±0.27	1.11±0.62	0.002
Kisspeptin (ng/ml)	Median (IQR)	0.68 (0.59–0.93)	2.71 (1.73–3.71)	<0.001
	Mean ± SD	0.73 ± 0.28	2.96 ± 1.84	0.001
Kisspeptin MoM	Mean ± SD	0.30 ± 0.12	1.22 ± 0.76	<0.001

Table 2 Shows kisspeptin levels in group A v/s group B was (0.73±0.28 v/s 2.96±1.84). Women with miscarriage had significantly lower serum kisspeptin concentration (p value <0.001) and hCG levels in women with miscarriage and women without miscarriage (48725.31±21933.20 v/s 97137.53±53745.46). In women with miscarriage hCG concentration was found significantly lower (p value 0.002).

ROC curve analysis was performed to determine the optimal cut-off values of significant variable (kisspeptin ng/ml) detected between the two groups. A optimal cut- off value of kisspeptin is 0.9735ng/ml (Positive if Less Than or Equal To); area under the curve (AUC) = 0.98 (95% CI - 0.957-1.000), with a sensitivity of 92.3 % and a specificity of 97.6%, was determined with standard error (SE) = 0.012, asymptotic sig. (p=0.000).

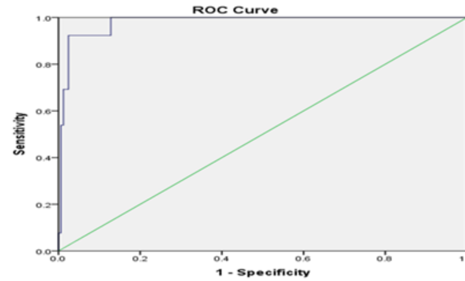

Figure 3: ROC curve for diagnostic performance of serum kisspeptin in women with miscarriage

Table 3: Sensitivity, Specificity of kisspeptin in women with miscarriage

Positive if less than or equal To	Sensitivity	1 – Specificity	Specificity	Yodon Index
0.9735	0.923	0.024	0.976	0.899

Table 3 illustrates the sensitivity, specificity, specificity (False positivity rate) of kisspeptin (ng/ml) at diverse level appropriate for miscarriage. As the level of kisspeptin (ng/ml) increases, sensitivity lessens and specificity enhances. The optimum cut off value was obtained by points of test values that grants the highest yodon Index that is (SN+SP)-1.

ROC curve analysis was performed to determine the optimal cut-off values of significant variable hCG (mIU/ml) detected between the two groups.A optimal cut- off value of hCG 77377.0 mIU/ml (positive if less than or equal to this value); area under the curve (AUC) = 0.792(95% CI - 0.706 - 0.877), with a sensitivity of 100 % and a specificity of 62.8 %, was determined with standard error (SE) = 0.043, asymptotic sig. (p =0.001).

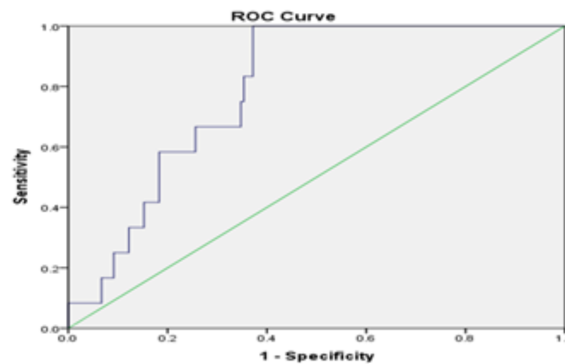

Figure 4: ROC curve of serum hCG (mIU/ml) in reference to miscarriage

Table 4: Sensitivity, Specificity of hCG in women with miscarriage

Positive if less than or equal to	Sensitivity	1 – specificity	Specificity	Yodon Index
77377.0000	1.000	0.372	0.628	0.628

Table 4 illustrates the sensitivity, specificity, 1- specificity (False positivity rate) of hCG (mIU/ml) at diverse level appropriate for miscarriage. As the level of hCG (mIU/ml) increases, specificity lessens and sensitivity enhances. The optimum cut off value was obtained by points of test values that grants the highest yodon Index that is (SN+SP)-1.

Discussion

The present study evaluated the association of serum kisspeptin levels with miscarriage among pregnant women in early gestation and demonstrated a significant reduction in serum kisspeptin levels in women who experienced miscarriage compared to those with viable pregnancies. These findings highlight the potential role of kisspeptin as a reliable biomarker for early prediction of adverse pregnancy outcomes.

In this study, the overall incidence of miscarriage was 7.3% (13 out of 178), which is slightly lower than the globally reported rates of 10–20% [1]. This variation may be attributed to differences in study population, inclusion criteria, and follow-up duration. The majority of participants were in the age group of 21–30 years, and maternal age did not show a statistically significant association with miscarriage, which is consistent with previous studies suggesting that age-related risk becomes more pronounced after 35 years [11].

Anthropometric parameters such as BMI and weight were marginally lower in the miscarriage group, although the difference was not statistically significant. Similar observations have been reported in earlier studies, indicating that mild variations in BMI within the normal range may not independently influence early pregnancy loss [12]. Likewise, vital parameters including systolic and diastolic blood pressure did not differ significantly between the two groups, suggesting that hemodynamic factors may not play a major role in early miscarriage among otherwise healthy women. Routine biochemical parameters, including renal function tests, liver enzymes, lipid profile, and blood glucose levels, did not show significant differences between the groups. These findings are in agreement with prior research indicating that conventional biochemical markers are not sensitive predictors of early pregnancy loss in asymptomatic women [13]. Haematological parameters also remained comparable between the groups, further supporting the limited utility of routine laboratory investigations in predicting miscarriage.

A key finding of this study was the significant association between serum kisspeptin levels and gestational age. Kisspeptin levels showed a progressive rise with increasing gestational age, with a moderate positive correlation ($r = 0.389$, $p < 0.001$).

This trend is consistent with previous studies demonstrating that circulating kisspeptin concentrations increase throughout early pregnancy due to placental secretion [6,14]. The trophoblastic origin of kisspeptin underscores its importance in placental development and function. In contrast, serum hCG levels showed a declining trend after the early peak and did not demonstrate a significant correlation with gestational age in this study. Although hCG is widely used as a marker of pregnancy viability, its variability and plateauing pattern limit its predictive accuracy when used alone [8,15]. Importantly, women who experienced miscarriage had significantly lower serum kisspeptin levels compared to those with ongoing pregnancies (0.73 ± 0.28 ng/mL vs 2.96 ± 1.84 ng/mL, $p = 0.001$). These findings are in strong agreement with previous studies by Armstrong et al. and Jayasena et al., which reported markedly reduced kisspeptin levels in miscarriage cases [7,9]. The reduced levels may reflect impaired trophoblastic invasion and placental insufficiency, which are key mechanisms underlying early pregnancy loss [16]. The diagnostic performance of serum kisspeptin in predicting miscarriage was excellent, with an AUC of 0.980, sensitivity of 92.3%, and specificity of 97.6% at a cut-off value of ≤ 0.9735 ng/mL. This indicates that kisspeptin is a highly accurate biomarker for early detection of non-viable pregnancies. In comparison, hCG showed a lower AUC (0.792) and specificity, although it demonstrated high sensitivity. These findings are consistent with earlier studies that have highlighted the superior predictive value of kisspeptin over traditional markers [10,17].

The strengths of the present study include its prospective design, well-defined inclusion criteria, and comprehensive biochemical evaluation. However, certain limitations must be acknowledged. The relatively small number of miscarriage cases may limit the generalizability of the findings.

Additionally, the study was conducted at a single center, and multicentric studies with larger sample sizes are needed to validate these results. Overall, the findings of this study support the role of serum kisspeptin as a sensitive and specific biomarker for early prediction of miscarriage. Its incorporation into routine antenatal screening protocols may help in early identification of high-risk pregnancies and enable timely clinical interventions.

Conclusion

Serum kisspeptin levels are significantly lower in women who experience miscarriage and show strong predictive accuracy. It is a sensitive and specific independent biomarker, superior to hCG for early prediction of pregnancy loss. Incorporation of kisspeptin in early antenatal screening may help identify high-risk pregnancies, though larger studies are needed for validation.

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