RESEARCH ARTICLE

A comparative study of serum Kisspeptin levels among women with Polycystic Ovary Syndrome and normal fertile women

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Abstract

Objective: To measure serum Kisspeptin levels in women with Polycystic Ovary Syndrome and compare it with that of normal fertile women.

Methods: A case-control study was done at Al-Yarmouk Teaching Hospital /Baghdad, Iraq for nine months duration from March 2019 to December 2019. It included 45 patients with Polycystic Ovary Syndrome (case group) and 45 fertile women at least having one child as (control group). Blood samples were obtained from all women in the study to measure luteinizing Hormone (LH), Follicular Stimulating Hormone (FSH). Anti-Müllerian Hormone (AMH), Thyroid Stimulating Hormone (TSH), Prolactin (PRL) and Kisspeptin. Random blood glucose was also esrimated in both groups and the results were compared.

Results: Mean of Kisspeptin levels in women with polycystic ovary syndrome was significantly higher than that in fertile women (312.8±88.55 versus 131.6±61.94 pg/ml, P= 0.001). Statistically significant moderate positive correlation were detected between Kisspeptin level and each of anti Müllerian hormone, luteinizing hormone and antral follicle count (R 0.443, 0.49 and 0.687 respectively) and statistical significant weak positive correlation were detected between Kisspeptin level and each of prolactin and thyroid stimulating hormone (R 0.256 and 0.245 respectively). Statistical significant moderate negative correlations was detected between Kisspeptin level and follicular stimulating hormone (R -0.394).

Conclusion: Kisspeptin level was significantly increased in women with PCOS. The cut point of kisspeptin level was 189 pg/ml in PCOS. Thus kisspeptin at level > 189pg/ml can be used to predict the diagnosis of PCOS.

Keywords: PCOS. Infertility. Kisspeptin. (JPMA 71: S-97 [Suppl. 8]; 2021)

Introduction

Polycystic Ovary Syndrome (PCOS) is a collection of various signs and symptoms, with mild manifestations in some, to severe disruption of endocrine, reproductive and metabolic function in others.[1] A link between chronic low grade inflammation and PCOS has been mentioned by some studies, but the causal relationship is still uncertain between obesity, insulin resistance, or the polycystic ovarian syndrome itself.[2,3] Fifty to seventy percent of women with PCOS have hyperinsulinaemia,[4] which is commonly recognized as an important threat for development of metabolic syndrome.[5] The pathophysiology of PCOS have many extra ovarian explanations, however ovarian dysfunction plays the major role.[1]

The crucial controller of the hypothalamic pituitary ovarian axis is pulsatile Gonadotropin Releasing Hormone (GnRH) secretion which determines the secretion pattern of the gonadotropins (FSH & LH), and subsequent gonadal functions.[6]

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Inspite of being LH dependent, the moderate increase of LH which characterizes PCOS, is not considered the primary cause of the high ovarian androgen level. The reason is the normal process of LH-induced desensitisation of theca cells.[7] Kisspeptin arose to have a directive role on fertility function.[8] Kisspeptin /Kiss-1receptor signalling was considered a major stimulus for the secretion of GnRH and gonadotrophins.[9]

This study was conducted to measure the serum kisspeptin level in women with PCOS and compare it with that of normal fertile women.

Patients and Methods

This is a case-control study conducted at Al-Yarmouk Teaching Hospital for nine months period from March to November 2019.

Approval of the proposal of the study was obtained from Scientific Council of Obstetrics and Gynaecology, Council of Iraqi Board of Medical Specialization.

Verbal informed consent was obtained from each participant before their enrolment in the study. Patients were collected from gynaecology and infertility outpatient clinics of Al-Yarmouk Teaching Hospital,

Baghdad. Women with complaints of primary or secondary infertility and with diagnosis of PCOS were included in the study.

The inclusion criteria comprised of age between 18 to 40 years. Case group had primary or secondary infertility diagnosed as PCOS according to Rotterdam Criteria.[10] The control group had apparently healthy fertile women.

The exclusion criteria were women with Cushing syndrome, thyroid disease, hyperprolactinaemia and those taking steroids.

The study included 45 patients with PCOS (case group) and 45 fertile women with at least one child as control group.

Detailed history including (demographic data, obstetrical history, history of infertility: primary or secondary, and duration of infertility, past medical and surgical history, family and drug history was noted.

A general examination inclusive of systemic examination and vital signs was performed.

Participants were classified according to BMI as[10]

• Normal ($\leq$ 24.99 kg/m^2)

• Overweight (25 - 29.99 kg/m^2)

• Obese ($\geq$ 30 kg/m^2)

• Waist - hip ratio (W/H ratio)[11] was calculated by dividing waist circumference by hip circumference.

Participants were classified according to W/H ratio:

• <0.85 (normal).

• $\geq$0.85 (overweight).

Blood samples were obtained early in the morning, following 10 hours of fasting using disposable syringes and saved in tubes containing heparin, followed by centrifugation at 3000 rpm for 10 min to isolate sera. Serum concentrations of FSH, LH, PRL, TSH and AMH were determined using electrochemiluminescence immunoassay. Kisspeptin level was measured by enzyme linked immunosorbent assay. Random blood glucose was also estimated.

Trans-vaginal ultrasound examination was done by trans-vaginal probe E8CS of LOGIQ P5 ultrasound equipment in the infertility outpatient clinic at Al-Yarmouk Teaching Hospital.

Statistical analysis: The data was analyzed using Statistical Package for Social Sciences (SPSS) version 25. Receiver operating characteristic (ROC) curve analysis was used for prediction of kisspeptin level as diagnostic of PCOS. The p-level less than 0.05 was considered significant. The sample size was not calculated scientifically.

Results

Ninety participants were included in the study. They were divided into two groups with 45 women with PCOS considered as the case group and 45 fertile women considered as the control group.

Kisspeptin biomarker: Table-1 shows that the mean Kisspeptin level in women with PCOS was significantly higher than that in healthy women (312.8±88.55 versus 131.6±61.94 pg/ml, P= 0.001).

As seen in Table-2, the cut off point of kisspeptin level, 189 pg /ml, was found to be a predictive factor for the diagnosis of PCOS. The area under the curve (AUC) in ROC curve (96.3%) performs well as a general measure of predictive accuracy. Kisspeptin level was 93% sensitive, 80% specific, and 86.7% accurate as a marker for prediction of PCOS.

Statistically significant moderate positive correlation were detected between kisspeptin level and AMH LH and AFC. Statistically significant weak positive correlation was detected between kisspeptin level and both of PRL and TSH. Statistically significant moderate negative correlation was detected between kisspeptin level and FSH. No statistical significant correlations (P $\geq$ 0.05) between kisspeptin level and Random Blood Glucose was observed, as shown in Table-3.

Table-1: Comparison between study groups by kisspeptin biomarker level.

	Group	N	Mean	SD	P value
Kisspeptin level (pg/ml)	PCOS	45	312.8000	88.55	0.001
	Control	45	131.6000	61.94	

Table-2: Diagnostic accuracy for test of PCOS.

Kisspeptin Cut-off value	TAUC	SE	P value	Sensitivity	Specificity	PPV	NPV	Accuracy
189 Pg/ml	.963	.019	0.001	93%	80%	82.4%	92.3%	86.7%

TAUC=total area under the curve, SE=standard error, PPV= positive predictive value, NPV= Negative predictive value.

Table-3: Correlation between kisspeptin level and certain variables.

Variables	Kisspeptin level (pg/ml)	
	R	P value
LH	.490**	0.001
FSH	-.394**	0.001
TSH	.245*	0.02
Prolactin	.256*	.015
RBG	.068	.522
AFC	.687**	0.001
AMH	.443**	0.001

Abbreviations: LH=Luteinizing hormone, FSH=Follicular stimulating hormone, TSH= Thyroid stimulating hormone, RBG=random blood glucose, AFC=Antral follicle count, AMH=Anti-Müllerian Hormone.

Discussion

The present study found that kisspeptin level in women with PCOS was significantly higher than that in healthy women (P= 0.001), which is in agreement with that of other studies as of Chen et al[12] Jeon et al[13] and Yilmaz et al[14] Gorkem et al[15] and Kaya et al[16] who in their studies found that kisspeptin increased in PCOS group compared to control group. A positive correlation of kisspeptin with LH and leptin levels in PCOS was mentioned by Emekci et al in 2016, the study found, no statistically significant difference in neither serum kisspeptin nor leptin in control group and PCOS group,[17] which is not in agreement with the current study.

According to what had been observed in this study, there was a significant moderate positive correlation between kisspeptin level and LH and also a significant moderate positive correlation between kisspeptin level and both of AMH and AFC. Katulski et al. found in their observational study (2018) on 71 patients with PCOS, a significant positive correlation between kisspeptin and LH concentrations that supported the suggestion that reproductive disturbance in PCOS could be caused by abnormal kisspeptin signals on hypothalamic GnRH secretion.[18]

Varikasuvu et al. (2019) in their meta-analysis of 12 studies on women with PCOS, found increased circulatory KISS-1 levels which was positively associated with AMH,[19] which is consistent with the current study.

Also Kaya et al. (2019) observed positive significant correlation of kisspeptin with both LH and AFC, but showed no statistical significant association between kisspeptin and AMH (P=0.81).[16]

The present study showed negative correlation between kisspeptin level and FSH which is in agreement with a study done by Gorkem et al. (2018).[15]

The results of the present study were comparable with those of Kaya et al. (2019) regarding statistical significant correlations between kisspeptin level and prolactin (P ≥ 0.05 and p=0.35).[16]

In the current study there was statistical significant correlation between kisspeptin and TSH. In a study done by Tomori et al. (2017) which assessed the role of kisspeptin in the disturbed secretion of gonadotropin in hypothyroid patienrs, kisspeptin expression in the ARC was inhibited due to a low thyroid hormone level, revealing that the dysregulation of reproductive function in hypothyroidism is due to the suppression of kisspeptin neurons in the ARC.[20]

Conclusion

Women with PCOs have significantly high levels of kisspeptin. The cut point of kisspeptin level was 189 pg/ml, so kisspeptin level > 189pg/ml is predictive for diagnosis of PCOS.

Limitation

The sample size was estimated according to local clinical case attendance to the hospital during the time of the study. It is acknowledged that a correct scientific method for sample size calculation was not used.

Disclaimer: None

Conflict of Interest: None.

Source of Support: None.

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