Section: Physiology

Original Research Article

STUDIES ON THE ASSOCIATION OF ENDOCRINE AND METABOLIC DISORDERS IN POLYCYSTIC OVARIAN SYNDROME

Kumari Tanuja[1], Dinesh Prasad[1], H. P Dubey[2]

[1]Tutor, Department of Physiology, JLNMC, Bhagalpur, Bihar, India
[2]Associate Professor, Department of Physiology, JLNMC, Bhagalpur, Bihar, India

Received : 25/04/2023
Received in revised form : 20/05/2023
Accepted : 04/06/2023

Keywords:
Endocrinological and Metabolic Disorder, Obese and Non-Obese Polycystic Ovarian Syndrome.

Corresponding Author:
Dr. Dinesh Prasad,
Email: drdineshprasad999@gmail.com

DOI: 10.47009/jamp.2023.5.5.56

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (5); 283-288

Abstract

Background: Polycystic ovarian syndrome (PCOS) is one of the most frequently encountered endocrine disorders in women in reproductive age. This condition occurs in as many as 5-10 % of women of reproductive age with onset manifesting as early as puberty. PCOS is primarily characterized by hyperandrogenism, insulin-resistance and chronic anovulation. **Materials and Methods:** PCOS patients (n = 50) were recruited from the out-patient department of the Department of Gynecology at the Jawahar Lal Nehru Medical College and Hospital, Bhagalpur, Bihar (JLNMCH) from January 2022 to December 2022. Based on the criteria derived from the 1990 National Institutes of Health (NIH) conference, diagnosis of PCOS was established when either oligomenorrhea (cycles lasting longer than 35 days) or amenorrhea (less than two menstrual cycles in the past 6 months) and either clinical signs of hyperandrogenism (hirsutism or obvious acne or alopecia and/or an elevated total testosterone (normal range: testosterone (total) <86ng/ml). **Result:** In our study we have taken 25 non- obese PCOS cases and 25 obese PCOS cases as cases and 25 non obese controls and 25 obese controls as control. Serum LH non-obese PCOS is higher obese PCOS and control. While serum FSH level between two groups is unaltered in all group. In non obese PCOS group serum mean LH/FSH ratio is higher than non-obese control and obese PCOS. LH and LH/FSH ratio are positively correlated with BMI. LH and LH/FSH ratio are negatively correlated with AGE. **Conclusion:** We can conclude that obese PCOS is more associated with insulin, testosterone level abnormalities and non obese PCOS is associated with gonadotrophin abnormalities.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is one of the most frequently encountered endocrine disorders in women in reproductive age.[1] This condition occurs in as many as 5-10 % of women of reproductive age with onset manifesting as early as puberty.[2,3] PCOS is primarily characterized by hyperandrogenism, insulin-resistance and chronic anovulation.[4] Chronic anovulation may present as irregular menstrual periods or amenorrhea. It is not essential to document anovulation by ultrasonography or progesterone measurements in the presence of a clear clinical history. In fact, PCOS occurs in 85 to 90% of women with oligomenorrhea and in 30-40% of women with amenorrhea.[5]

In obese PCOS women, sex hormone binding globulin (SHBG) levels are decreased (a well-known effect of obesity per se) and this leads to an increase in free testosterone levels. Furthermore, insulin is a negative regulator of the production of SHBG by the liver,[6] and SHBG levels are decreased in hyperinsulinemic conditions such as metabolic syndrome and visceral obesity.[7,8]

Hyperandrogenism is usually suggested by the presence of hirsutism (occurs in approximately 80% of PCOS women) and can be documented by measuring androgen levels in the blood. Free testosterone is the most frequently elevated steroid in the blood in PCOS. Circulating levels of total testosterone, androstenedione and Dehydroepiandrosterone (DHEA) are also elevated.[9]

The etiology of PCOS is still obscure. It has been well documented that inappropriate gonadotrophin secretion, especially high luteinizing hormone (LH) secretion, is associated with the classic form of PCOS.[10,11]

LH/FSH ratio of more than 2 was part of the diagnostic criteria of PCOS. Women with PCOS have higher mean concentrations of LH, increased bioactivity of LH and low to low-normal levels of follicle stimulating hormone (FSH).[12,13]

ISSN (O): 2687-5365; ISSN (P): 2753-6556

PCOS is one of the commonest causes of infertility in females. It is known that anovulation or decreased ovulation is the primary cause of this infertility and as mentioned above, both metformin and TZD increase the rates of ovulation.

Aims and Objectives: In the view of such conflicting reports objective of this study is to know

1. The endocrine and metabolic alteration in patient with PCOS
2. To further characterize this metabolic alteration with changing age, BMI (Obese and Non-obese), ethnicity.

MATERIALS AND METHODS

PCOS patients (n = 50) were recruited from the out-patient department of the Department of Gynecology at the Jawahar Lal Nehru Medical College and Hospital, Bhagalpur, Bihar (JLNMCH) from January 2022 to December 2022. Based on the criteria derived from the 1990 National Institutes of Health (NIH) conference, diagnosis of PCOS was established when either oligomenorrhea (cycles lasting longer than 35 days) or amenorrhea (less than two menstrual cycles in the past 6 months) and either clinical signs of hyperandrogenism (hirsutism or obvious acne or alopecia and/or an elevated total testosterone (normal range: testosterone(total) <86ng/ml)., were found, and other ovarian, thyroid diseases & hyper-prolactinemia, that may be associated with oligomenorrhea and/or hyperandrogenism, were excluded. Oligoovulation or anovulation is usually associated with oligo-menorrhea or amenorrhea If serum testosterone is > 200ng/dl, the case may be due to ovarian tumor. Hirsutism was routinely graded by two physicians independently using the common modified Ferriman–Gallwey (FG) score. FG scores never differed by more than 2 and when not identical were re-evaluated by a third physician and the median value used. This method to assess hirsutism requires the visual scoring of the extent of terminal hairs in nine body areas, namely (a) upper lip, (b) chin, (c) chest, (d) upper abdomen, (e) lower abdomen, (f) upper back, (g) lower back, (h) thighs and (i) upper arms. The lower arms or lower legs are not included in the hair assessment. Each area is scored from 0 to 4, resulting in a possible maximum score of 36. Hirsutism was diagnosed when a score above 5 was evaluated. Childhood onset hirsutism cases excluded from study because that cases may be due to congenital adrenal hyperplasia all recruited women were otherwise healthy. Healthy controls (n = 50) were taken with a subgroup of lean PCOS, BMI< 25kg/m2 women (n = 25) and obese PCOS, BMI ≥30 kg/m2. Controls were recruited from a group without oligomenorrhea or sign of hyperandrogenism. PCOS as well as control subjects had not taken any medication known to affect carbohydrate metabolism or endocrine parameters for at least 3 months before entering the study. Women taking contraceptive pills were also excluded from the study.

Data Collection

In PCOS subjects and control women, clinical parameters were assessed by physical examination, including the degree of hirsutism by evaluating the FG score and anthropometric measurements including body weight in kg (BW) and height in cm. BMI was calculated as weight/(height)2 (kg/m2). Parameters of insulin resistance were evaluated using fasting glucose to insulin ratio (glucose in mg/dl and insulin in iu/ml. After an overnight fast of 12 h, patients had their glucose and insulin levels determined. Except for amenorrhoic women, all laboratory determinations were performed in the 3rd day of the menstruation cycle.

Biochemical Assays

Automated chemiluminescence immunoassay systems were used for the determination of LH, FSH, testosterone, thyrotropin (TSH), cholesterol (CHOL), triglycerides (TG) and blood glucose (G), insulin . Different parameters described detail in below.

RESULTS

In our study we have taken 25 non- obese PCOS cases and 25 obese PCOS cases as cases and 25 non obese controls and 25 obese controls as control. Details of cases and controls described in table. Serum LH non-obese PCOS is higher obese PCOS and control. While serum FSH level between two groups is unaltered in all group. In non obese PCOS group serum mean LH/FSH ratio is higher than non-obese control and obese PCOS. LH and LH/FSH ratio are positively correlated with BMI. LH and LH/FSH ratio are negatively correlated with AGE. Our PCOS population reflects the syndrome heterogeneity: we found that low (< 4.5) fasting G/I ratio affected 22% cases of non-obese PCOS, while in obese-PCOS percentage is 75%. While in obese control percentage is 25% and non-obese control no cases of low fasting G/I ratio. Serum fasting insulin level (mean) is higher in obese PCOS than both obese control and non obese PCOS. In obese PCOS group serum fasting G/I ratio (mean) is higher than both non-obese PCOS and obese control. Serum total testosterone level (mean) is higher in obese PCOS than both obese control and non obese PCOS. PCOS is associated with raised level of VLDL and TG level and these are positively correlated with age.

Table 1: Age & BMI of Study Population

Age/BMI		Non-obese PCOS	Obese PCOS	Obese Control	Non-obese Control	Overweight PCOS
Age in Years	Range	20-35	20-35	20-35	20-35	20-25
	Mean	25.09	29.25	29.35	25	21.87
	Sd	5.05	2.73	3.59	3.6	1.8

ISSN (O): 2687-5365; ISSN (P): 2753-6556

BMI Kg/m2	Range	19-24.9	30-35	30-35	19-24.9	25-29.9
	Mean	21.35	32.02	32.32	22.49	26.7
	Sd	1.54	1.93	1.59	1.87	1.45

Table 2: Hormonal Status of Non-Obese Individuals with PCOS (BMI < 25 kg/m2) in Comparison to BMI Match Control and Their Statical Significance

Hormones	**NON-OBESE PCOS n = 25 Mean ± SD**	**Non-Obese Control n= 25 Mean±SD**	**Statical Analysis Between PCOS and control groups If p < 0.05 it is statically significant**	
			P value	**Whether statically significant or not**
LHiu/ml	12.189±6.26	3.98±0 .71	P < .001	Significant
FSH iu/ml	4.598±1.756	4.67±1.37	P= 0 .88	Not significant
LH/FSH RATIO	2.64±.861	0 .95±.0. 28	P < .001	Significant
Fasting glucose mg/dl	85.23±7.5	84.6±7.79	P = .789	Not significant
Fasting insulin uIu/ml	15.7±6.24	8.68±4.18	P= .0001	Significant
Fasting Glucose/insulin ratio Mg/dl/iu/ml	6.16±2.39	12.03±5.36	P = .001	Significant
Total testosterone ng/dl	77.52±31.04	19.902±10.22	P<0.001	Significant

n = number of cases

We compare different parameter in between non-obese PCOS group and BMI match control we found in that in [Table 2].

Table 3: Serum lipid profile in individuals with non-obese PCOS (Bmi < 25 kg/m2) in comparison to non-obese PCOS (BMI < 25 kg/m2) and their statical significance

Lipids mg/dl	**NON- Obese PCOS n = 25 Mean ± SD**	**NON- OBESE Control n= 25 Mean±SD**	**Statical analysis between obese PCOS and non-obese groups if p value<0.05 it is statically significant**	
			P value	**Whether significant or not**
Total cholesterol	167.18±21.31	169.6±16.8	P =.68	Significant
VLDL	22.86±6.3	19.35±2.87	P= 0 .02	Significant
LDL	99.72±13.6	101.45±17.35	P = .72	Significant
HDL	44.23±4.73	48.8±4.85	P = .0036	Significant
Triglyceride	114.32±31.52	96.8±14.2	P= .025	Significant

n = number of cases

VLDL very low density lipoprotein
LDL low density lipoprotein
HDL high density lipoprotein
We compare lipid profile in between non-obese PCOS group and BMI match control we found in that in [Table3]

Table 4: correlation between Bmi and other dependent variable

Dependent variable	**r value**	**p value**
LH	-0.389	<0.01
FSH	-0.122	> 0.1 NS
LH/FSH	-0.399	<0 .01
GLUCOSE	0.07	> 0.05
INSULIN	0.545	< 0 .001
Glucose/Insulin Ratio	-0.38	< 0.01
Testosterone	0.302	< 0.05
Total Cholesterol	0.4	< 0 .01
VLDL	0.473	<0 .001
LDL	0.388	<0 .01
HDL	-0.454	< 0 .001
TG	0.476	< 0 .001

[Table 4] shows correlation for BMI and other following parameters (r value and p value)

Table 5: correlation between age and other dependent variable

Dependent variable	**r value**	**p value**
LH	-0.517	<.001
FSH	-.016	> 0.05
LH/FSH	-0.782	<0 .001
GLUCOSE	0.02	>0.05
INSULIN	0.032	>0.05
Glucose/Insulin Ratio	.142	>0.05
Testosterone	-0.027	>0.05
Total Cholesterol	0.252	>0.05
VLDL	0.284	< .05

ISSN (O): 2687-5365; ISSN (P): 2753-6556

LDL	0.196	>0.05
HDL	-0.O76	>0.05
TG	0.289	< .05

[Table 5] shows correlation for age and other following parameters(r value and p value)

DISCUSSION

In our study mean serum concentration of LH of 22 non-obese PCOS is higher than 20 obese PCOS and statically significant (p < .01) while serum FSH level between two group is not statistically significant (p=.651) and LH/FSH ratio is higher in non-obese group than obese group and it is statistically significant (p=.0005 i.e. value < .05). If we compare this value between PCOS group and BMI match control we found that in non-obese PCOS group serum LH level is higher than non-obese control and it is statically significant (p value < .001). Serum LH level is also higher in obese PCOS than obese control and it is statically significant (p value < .001). Serum FSH level is unaltered in non-obese PCOS than non-obese control and it is statically insignificant (p value = .651 i.e. <.05). Serum FSH level is also unaltered in obese PCOS than obese control and it is statically insignificant (p value = .642 i.e. <.05). In non obese PCOS group serum mean LH/FSH ratio is higher than non-obese control and it is statically significant (p value < .001). Serum mean LH/FSH ratio is also higher in obese PCOS than obese control and it is statically significant (p value < .001).

In our study Elevated LH/FSH ratio (LH/FSH>2) was found only in 77% of the studied non-obese PCOS women (17 cases out of 22). Elevated LH/FSH ratio (LH/FSH>2) was found only in 45% of the studied obese PCOS women (9 cases out of 20). Serum LH and LH ratio are strongly negatively correlated, BMI: LH (r = -0.389, p < 0.01), LH/FSH ratio (r= - 0.399 , p< 0.1).

The earlier study carried out by Maria C. Garcia et al. 2001 that lean PCOS (BMI <25kg/m2) are associated with higher LH/FSH ratio. 2.47±.04 Vs .66±.0.08) and statically highly significant (p<0.001). PCOS are associated with higher serum LH/FSH ratio and LH concentration are claimed by several study but whether BMI is inversely correlated with serum LH concentration and LH/FSH has conflicting report. That is consistent with our study.

Miriam E. Silfen et al 2003,[14] also observed similar result. BMI correlated strongly and inversely with pool and LH pulse amplitude but not with LH pulse frequency (Morales et al., 1996 ; Arroyo et al., 1997).(242-243) All these data raise the possibility that an obesity-associated factor may suppress the GnRH pulse amplitude or pituitary LH responsivity.

Clinical studies have repeatedly shown that obese PCOS women are characterized by significantly lower LH concentrations than their normal-weight counterparts and that, in very obese PCOS women, LH concentrations frequently resemble the normal range.

Endorphin

PCOS women are characterized by increased levels of plasma immunoreactive -endorphin.[15]

Obesity by itself is characterized by an increased opioid system activity.[16] Moreover, infusion of physiological doses of -endorphin has been found to induce a significant increase in insulin concentration in obese but not in normal-weight subjects, suggesting cell hypersensitivity to opioids in the obese state.[17]

Insulin resistance- Over the last 10 years there has been increasing interest in the role of insulin and growth factors in patients with PCOS. Obesity associated with insulin resistance and hyperinsulinaemia are well-recognized features of this syndrome; however, changes in insulin concentrations have also been reported in lean subjects by several authors (Dunaif et al., 1988; Fulghesu et al., 1995).[18]

Our PCOS population reflects the syndrome heterogeneity: we found that low (< 4.5) fasting G/I ratio(glucose in mg/dl divided by insulin in uIu/ml) affected 22% (5cases out of 22cases) cases of non-obese PCOS, while in obese-PCOS percentage is 75%. (15 cases out of 20 cases) while in obese control percentage is 25% (5cases out of 20) and non-obese control no cases of low fasting G/I ratio. Fasting G/I ratio <4.5 signifies insulin resistant.

Serum fasting insulin level (mean) is also higher in obese PCOS than non-obese PCOS and it is statically significant (p value = .0002). In obese PCOS group serum fasting G/I ratio (mean) is higher than non-obese PCOS and it is statically significant (p value = .01). Serum fasting insulin level is positively correlated, BMI: Insulin (r = 0.545, p < 0.001), fasting G/I ratio negatively correlated (r= - 0.399 , p< 0.01).

Miriam E. Silfen 2003, observed Fasting glucose and HgbA1c levels were similar in the three study groups i.e. obese PCOS, obese control and non-obese PCOS and none of the subjects had impaired fasting glucose or diabetes.

Lewy et al,[19] previously reported that obese adolescent girls with PCOS (mean age 12 years old, BMI 33 kg/m2) had higher insulin resistance as measured by hyperinsulinemic-euglycemic clamp than those who were matched for age, percent body fat and abdominal fat without PCOS.[20]

The bulk of these observations indicate that hyperinsulinaemia in obese PCOS subjects is due to two factors: one characteristic of PCOS, and the other obesity-specific.

Dyslipidemia

In our study mean fasting serum concentration of total cholesterol of obese PCOS (mean) is higher than non-obese PCOS and statically significant

ISSN (O): 2687-5365; ISSN (P): 2753-6556

(p=0.0036, i.e. p < .01) while serum VLDL level (mean) between two group is statistically significant(p=0.00056 i.e.<.o1) and higher in obese group. LDL, TG also higher in obese group in comparison to non-obese PCOS and HDL is lower in obese PCOS than non-obese PCOS. .In obese PCOS is higher than non-obese PCOS and statically significant (p=0.0065, i.e. p < .01) while serum TG level (mean) between two group is statistically significant (p=0.00o48 i.e.<.o1) and higher in obese group .In obese PCOS HDL is (mean) is lower than non-obese PCOS and statically significant (p=0.0033, i.e. p < .01).

If we compare this value between PCOS group and BMI match control we found that in non obese PCOS group serum fating TG level (mean ± SD) only is higher than non-obese and serum HDL is lower in non-obese PCOS in comparison to non-obese control. In obese PCOS similar result obtained when compared to obese control.

In our study lipid fraction also correlated with BMI. TC (r=0.4,p<.01) VLDL (r=0.473 p<0.001), LDL(r=0.388,p<0.01) TG (r=0.476,p<0.001) are positively correlated and HDL (r=-0.476,p<0.001) negatively correlated.

Contrasting reports available among different study groups. Yilmaz et al,[21] observed that Serum fasting TC, LDL-C, TG, Apo B, levels were similar between PCOS and control groups. Lp(a) levels were higher in PCOS patients than in control subjects, whereas HDL-C and Apo A levels were lower. Compared with obese PCOS subjects, non-obese PCOS subjects had low TC, LDL-C, TG, Apo B, Lp(a) and Serum HDL-C and Apo A levels were similar between obese and non-obese women with PCOS. Levels of HDL-C and Apo A were lower in both obese and non-obese PCOS patients than in obese and non-obese control subjects, whereas Lp(a) levels were higher. No correlation was observed between plasma Hcy, body mass index, serum TC, LDL-C, HDL-C, Apo A, Apo B and Lp(a) levels.

Miriam E. Silfen et al. 2003, observed Lower LDL and higher HDL cholesterol was noted in the nonobese compared with the obese adolescents with PCOS. No differences in lipid levels were detected between the obese study groups.

Some studies have reported increased hyperandrogenism in obese compared with nonobese women with PCOS, as evidenced by a higher total and/or free testosterone or free androgen index, but comparable and DHEAS levels.[22]

Consistent with the diagnosis, the obese PCOS group had higher levels of total testosterone, compared with BMI-matched controls and also non-obese PCOS.

Age related changes of different hormonal and biochemical parameter in PCOS.

In our study LH and LH/FSH ratio is decreased with age and VLDL and TG is increased with age. It is expected that as PCOS is associated with raised VLDL and TG level, it will be raised in advancing age, but why LH level is decreased can be explained that in advancing age inhibin level is increased.[23] Other studies reported a rise in LH,[24] in advancing age, so this is consistent with our study. The inverse relationship between age and LH in the current study in anovulatory women is unexpected and surprising. A statistically significant decrease in LH levels was also observed when young women were compared with those above 30 years of age. In a recent 10-year follow-up study gonado-trophin levels were significant reduced in PCOS.[25]

CONCLUSION

PCOS has been one of the most explored and controversial areas in reproductive medicine. So is a subject of continuous studies concerning both pathogenesis, diagnostics methods, and therapeutics procedures. It is associated with endocrine and metabolic abnormalities.

We can conclude that obese PCOS is more associated with insulin, testosterone level abnormalities and non-obese PCOS is associated with gonadotrophin abnormalities.

REFERENCES

1. Lobos R,Carmina E,The importance of diagnosis poly cystic ovarian syndrome,Ann intern med 2016:989-993
2. Sozen I,Aricia Hyperinsulinism and its interaction with hyperandrogenism in polycystic ovarian syndrome,obs gyn surv 2011;55;321-328
3. Zborowski JV,Cauley JA,TalbottEO,et al.Clinical Review 116;Bone mineral density,androgen,and the polycystic ovary:the complex and controversial issue of androgenic influence in female bone,J CLIN.END.META. 200:85:3496-3508
4. Barnses R,Rosenfield RL,The polycystic ovarian syndrome; pathogenesis and treatement,Ann intern Med 2016;110:386-399.
5. Achard C,Thiers J,Le virilsme et son association a l'insuffience glycolytique,Buil Acad Nati Med 2020;86;51-83.
6. Stein IF,Leventhal ML,:Amenorrhea associated with bilateral polycystic ovaries.Am J obs gyn 1935:29:181-191.
7. Goldzieher MW.2green JA,(2012):1.CLINICAL 2.HISTOLOGICAL. Jclin eodo.Meta(22)325-338.
8. Franks S, White DM. Prevalence of and etiological factors in polycystic ovarian syndrome. Ann N Y Acad Sci 2013;687:112-4.
9. J Postgrad Med 2014;50:140-4 Insulin resistance, insulin sensitization and inflammation in polycystic ovarian syndrome Dhindsa G, Bhatia R, Dhindsa M, Bhatia
10. Yki-Jarvinen H, Makimattila S, Utriainen T, Rutanen EM. Portal insulin concentrations rather than insulin sensitivity regulate serum sex hormone-binding globulin and insulin-like growth factor binding protein 1 in vivo. J Clin Endocrinol Metab 2015;80:3227-32.
11. Haffner SM, Karhapaa P, Mykkanen L, Laakso M. Insulin resistance, body fat distribution, and sex hormones in men. Diabetes 2014;43:212-9.
12. Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Salonen R et al. Sex hormones, inflammation and the metabolic syndrome: a population based study. Eur J Endocrinol 2013;149:601-8.
13. Barnes R, Rosenfield RL, Burstein S & Ehrmann D (1989b). "Pituitary-ovarian responses to nafarlin testing in the polycystic ovary syndrome." N J Med 32(9): 559-565.
14. IbanezL, HalJE, PotauN, CarascosaA, PratN&TaylorAE(1996) Ovarian17-hydroxyprogesterone hyperesponsivenes to gonadotropin-releasing hormone(GnRH) agonist challenge in women with polycystic

ISSN (O): 2687-5365; ISSN (P): 2753-6556

ovary syndrome is not mediated by luteinizing hormone hyper secretion: evidence from GnRH agonist and human chorionic gonadotropin stimulation testing. J Clin EndocrinolMetab81(1):4103-4107.
15. GilingSmithC, WilisDS & Franks S (197b) Oestradiol feedback stimulation androgen biosyn-thesis by human theca cells.HumReprod12(8):1621-1628.
16. LevrantSG,Barnes RB,RosenfieldRL(1997) A pilot study of the human chorionic gonadotrophin test for ovarian hyperandrogenism.HumReprod12(7):1416-1420
17. McArthur JW, IngersolFM & WorcesterJ (1958)Theurinary excretionofinterstitial-cel andfollicle stimulating hormone activity by women with diseases of the reproductive system. J ClinEn-docrinol Metab18:1202-1215.
18. YenSS,VelaP &RankinJ(1970)Inappropriate secretion off olicle-stimulating hormone and lutei-nizing hormone in polycystic ovarian disease.J Clin Endocrinol Metab30(4):435-42.
19. Havisto AM, Peterson K, Bergendahl M, Virkamaki A & Huhtaniemi I (1995) Ocurence and biological properties of a common genetic variant of luteinizing hormone. JClinEndocrinolMetab 80(4):1257-1263.
20. Rajkhowa M, Talbot JA, Jones PW, PetersonK, Havisto AM, HuhtaniemiI & Clayton RN (2005)Prevalence of an immunological LH beta-subunit variantin a UK population of healthy women and women with polycystic ovary syndrome. ClinEndocrinol 43(3):297-303
21. Venturoli S, Porcu E, Fabbri R, Magrini O, Gammi L, Paradisi R, et al. Episodic pulsatile secretion of FSH, LH, prolactin, oestradiol, oestrone, and LH circadian variations in polycystic ovary syndrome. Clin Endocrinol (Oxf) 2018;28:93-107.
22. Kletzky OA, Davajan V, Nakamura RM, Thorneycroft IH, Mishell DR, Jr. Clinical categorization of patients with secondary amenorrhea using progesterone-induced uterine bleeding and measurement of serum gonadotropin levels. Am J Obstet Gynecol 2015;121:695-703.
23. Arroyo A, Laughlin GA, Morales AJ, Yen SS. Inappropriate gonadotropin secretion in polycystic ovary syndrome: influence of adiposity. J Clin Endocrinol Metab 2020;82:3728-33.
24. Mason HD, Margara R, Winston RM, Seppala M, Koistinen R, Franks S. Insulin-like growth factor-I (IGF-I) inhibits production of IGF-binding protein-1 while stimulating estradiol secretion in granulosa cells from normal and polycystic human ovaries. J Clin Endocrinol Metab 2021;76:1275-9.
25. Homburg R, Eshel A, Kilborn J, Adams J, Jacobs HS. Combined luteinizing hormone releasing hormone analogue and exogenous gonadotrophins for the treatment of infertility associated with polycystic ovaries. Hum Reprod 2022;5:32-5.

ISSN (O): 2687-5365; ISSN (P): 2753-6556