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ORIGINAL ARTICLE

Association of LH/FSH Ratio with Thyroid Stimulating Hormone and Prolactin Levels in Women with Polycystic Ovarian Syndrome in Pakistan

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ABSTRACT

Objective: The aim of our study is to find the association of Luteinizing Hormone/Follicle Stimulating Hormone ratio (LH/FSH ratio) with Thyroid Stimulating Hormone (TSH) and prolactin levels in women with Polycystic Ovarian Syndrome (PCOS).

Methods: An observational cross-sectional study was conducted in the gynecology and endocrine outpatient departments of Darul Sehat hospital from March to December 2019. The demographic data were noted, and lab investigations were done on 2nd and 3rd day of menstrual cycle. All cases were divided into 2 groups, one with LH/FSH ratio ≤2 and other >2. All females of reproductive age 15-44 years who were diagnosed with PCOS according to Rotterdam criteria were included.

Results: Of 130 women, the mean age was 26.16 ± 5.81 years. There were 103 (79.2%) women found with LH/FSH ≤ 2 and 27 (20.8%) with LH/FSH > 2. Mean difference of TSH was found significantly higher in PCOS women with LH/FSH > 2 as compared to LH/FSH ≤ 2 i.e., 3.74 ± 6.49 vs. 2.32 ± 1.54 respectively (p-value 0.049). While an insignificant mean difference of PCOS with LH/FSH was found with prolactin (p-value 0.536) and insulin (p-value 0.902). A significantly weak positive correlation of prolactin was found with LH/FSH ratio (r: 0.191, p-value 0.029).

Conclusion: A significant correlation was found between LH/FSH ratio and TSH levels in women with PCOS which justifies the need for further evaluation. Therefore, thyroid function should be assessed in women with PCOS with raised LH/FSH ratio which would help in management.

Keywords: Follicle Stimulating Hormone, Luteinizing Hormone, Prolactin, Polycystic Ovary Syndrome, Thyroid Stimulating Hormone.

INTRODUCTION

In reproductive age women, most prevalent and most researched endocrine disorder is polycystic ovary syndrome (PCOS). It is a diverse condition marked by persistent ovulatory dysfunction and hyperandrogenism. The prevalence of this disorder is around 5% to 15%. PCOS is diagnosed on the basis of standard criteria defined by European Society of Human Reproduction and Embryology American Society for Reproductive Medicine.[1] Dysfunction of ovaries and increased androgen are the central source of the disease, but other factors, such as obesity and environmental factors also affect the occurrence of separate features.[2,3] The pathophysiology of polycystic ovarian disease is mainly due to irregularity of the hypothalamic -pituitary-ovarian or adrenal axis. A disruption in the secretion pattern of the gonadotropin-releasing hormone (GnRH) causes the relative rise in Luteinizing Hormone (LH) to Follicle Stimulating Hormone (FSH) discharge.[4] An increase in LH release is caused by abnormal feedback of ovarian estrogen.[5] Usually, in healthy women, the LH and FSH ratio usually comes between 1 and 2. In polycystic ovarian disease, this ratio may reach as high as 2 or 3.[6] It is related to the significant gynecological conditions which includes infertility, menstrual irregularities (prolonged cycles) and recurrent miscarriages.[7] Studies have shown a link between PCOS and hyperprolactinemia due to overlapping clinical features and complex pathophysiology but other causes of hyperprolactinemia need to be excluded first.[8] Early studies showed

elevated serum prolactin levels in patients with polycystic ovaries. However, recent studies that excluded transient elevations of prolactin using serial serum sampling, have shown a less frequent association of these disorders.[9] One of the study stated that hyperprolactinemia in PCOS can be due to macroprolactinemia, or pituitary adenoma and idiopathic hyperprolactinemia so is it worth doing magnetic resonance imaging (MRI) pituitary to rule out causes of hyperprolactinemia in our patients.[10]

An extensive literature search was done to evaluate the prevalence of subclinical hypothyroidism in women with polycystic ovaries. The results of the meta analysis showed that women with polycystic ovaries are prone to develop subclinical hypothyroidism.[11]

Another study conducted by Fatima M et al also showed association of subclinical hypothyroidism with PCOS and this in turn have shown to aggravate Insulin resistance.[12]

Considering the overlapping of clinical characteristics and pathophysiology of hypothyroidism and hyperprolactinemia in PCOS, we have conducted this study to observe the impact of prolactin and Thyroid Stimulating Hormone (TSH) on LH/FSH ratio patterns in PCOS in Pakistani cohort living in metropolitan city Karachi. The aim of our study is to find the association of LH/FSH ratio with the TSH and prolactin levels in our patients with PCOS.

METHODS

This was an observational cross-sectional study conducted in Gynecology and Endocrine outpatient departments of Darul Sehat Hospital from March 2019 to August 2019. The study was approved by the ethical review board, (RB-02/LCMD /01/2018) after taking verbal informed consent from the participants' data collection was commenced.

Sample size of 126 was calculated by using WHO calculator with prevalence of PCOS as 20%[4] and precision of 0.07. However, we enrolled 130 women. Sampling technique was nonprobability convenience sampling. All females of reproductive age 15-44 years enrolled in study who were diagnosed as having PCOS according to Rotterdam criteria, at least two out of three of the following: Oligomenorrhea/amenorrhea, hyperandrogenism (clinical or biochemical), Polycystic ovaries on ultrasound and exclusion of other disorders (androgen excess and ovulatory disorders).[13] The patients aged above 45 years, with diabetes, and known thyroid disorders were excluded. Biochemical tests were done on 2nd or 3rd day of menstrual cycles. Under aseptic measures 5 ml of fasting blood sampling was collected by venipuncture. LH, FSH, TSH, Prolactin, Fasting Insulin and testosterone levels were measured. All cases of PCOS were divided into 2 groups one with LH/FSH ratio ≤ 2 and other > 2 and their association with prolactin and TSH levels were observed. LH / FSH is usually between 1 and 2 in normal women while in women with PCOS this might raise to 2 or 3.[14] Prolactin <500 mU/l, thyroid function, thyroid-stimulating hormone 0.5–5 IU/l and should be measured in women with menstrual irregularities.[15]

Data entry and analysis were done using Statistical Package for Social Sciences (SPSS) version 20.0. Mean ± SD were computed for quantitative variables like, age and BMI while frequency and percentages were computed for categorical variables of like, marital status, menstrual irregularities, complications, and comorbidities. Inferential statistics were explored using independent t-test to compare mean difference of TSH and prolactin with LH/FSH ratio stratified on the basis of clinical characteristics. Moreover, Pearson correlation used to see association of LH/FSH ratio with prolactin and TSH. The p-value of ≤ 0.05 was considered statistically significant.

RESULTS

Of 130 women, the mean age was 26.16 ± 5.81 years. The mean height, weight and BMI of the patients was 1.55 ±0.05 m, 66.34 ± 14.89 kg, 27.46 ± 5.67 kg/m^2 respectively. There were 73 (56.2%) married and 57 (43.8%) unmarried women. Menstrual irregularities of women were found in 101 (77.7%) women. However, LH/FSH ≤ 2 was found in 103 (79.2%) women. Majority of the women were found with complications of PCOS i.e., 92 (70.8%).

Mean difference of TSH was found significantly higher in PCOS women with LH/FSH > 2 as compared to LH/FSH ≤ 2 i.e., 3.74 ± 6.49 vs. 2.32 ± 1.54 (p-value 0.049). While an insignificant mean difference of PCOS with LH/FSH was found with prolactin (p-value 0.536) and insulin (p-value 0.902). (Table 1)

Among patients with comorbidities, the mean TSH value of LH/FSH > 2 was found significantly higher as compared to LH/FSH ≤ 2 i.e., 6.34 ± 10.83 vs. 2.54 ± 1.59 (p-value 0.044). Moreover, among patients without complications of PCOS, the mean prolactin value of LH/FSH > 2 was found significantly higher as compared to LH/FSH ≤ 2 i.e., 34.82 ± 23.81 vs. 17.52 ± 9.13 (p-value 0.003).

An insignificant mean difference of TSH was found with menstrual regular cycle (p-value 0.081), menstrual

Table 1: Different endocrine parameters in the study group(n = 130)

Parameter	PCOS with LH/FSH ≤ 2	PCOS with LH/ FSH >2	p-value
TSH (µIU/mL) (n= 130)	2.32 ± 1.54	3.74 ± 6.49	0.049*
Prolactin (ng/mL) (n= 130)	29.10 ± 53.78	22.57 ± 16.47	0.536
Insulin (µIU/mL) (n= 85)	15.81 ± 9.90	15.50 ± 8.90	0.902

TSH: Thyroid stimulating hormone, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, PCOS: Polycystic ovary syndrome

Independent t-test applied, *p-value ≤ 0.05

Table 2: Mean difference of TSH and prolactin with LH/FSH ratio stratified on the basis of clinical characteristics (n = 130)

	TSHuIU/mL			Prolactin ng/mL		
	Mean ± SD	p-value	95% C.I	Mean ± SD	p-value	95% C.I
Menstrual Regular Cycle (n=29)						
LH/FSH ≤ 2	2.01 ± 0.92	0.081	-1.91 to 0.11	21.59 ± 19.37	0.750	-13.64 to 18.72
LH/FSH > 2	2.90 ± 1.69			19.05 ± 13.17		
Menstrual Irregular cycle (n=101)						
LH/FSH ≤ 2	2.41 ± 1.66	0.082	-3.32 to 0.20	31.12 ± 59.75	0.354	-10.33 to 3.72
LH/FSH > 2	4.05 ± 7.56			23.80 ± 17.62		
Complications (n=92)						
LH/FSH ≤ 2	2.40 ± 1.5	0.072	-3.53 to 0.14	22.11 ± 16.34	0.326	-3.87 to 11.54
LH/FSH > 2	4.09 ± 7.39			18.28 ± 10.85		
Without Complications (n=38)						
LH/FSH ≤ 2	2.15 ± 1.59	0.550	-1.67 to 0.87	17.52 ± 9.13	0.003*	-28.16 to -6.42
LH/FSH > 2	2.56 ± 0.94			34.82 ± 23.81		
Comorbidities (n=46)						
LH/FSH ≤ 2	2.54 ± 1.89	0.044*	-7.49 to -0.11	19.28 ± 8.89	0.132	-1.48 to 10.94
LH/FSH > 2	6.34 10.83			14.55 ± 4.80		
Without Comorbidities (n=84)						
LH/FSH ≤ 2	2.20 ± 1.30	0.645	-0.83 to 0.50	21.54 ± 17.08	0.281	-14.26 to 4.19
LH/FSH > 2	2.36 ± 1.19			26.57 ± 18.79		

C.I: Confidence interval, TSH: Thyroid stimulating hormone, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone

Independent t-test applied, *p-value ≤ 0.05

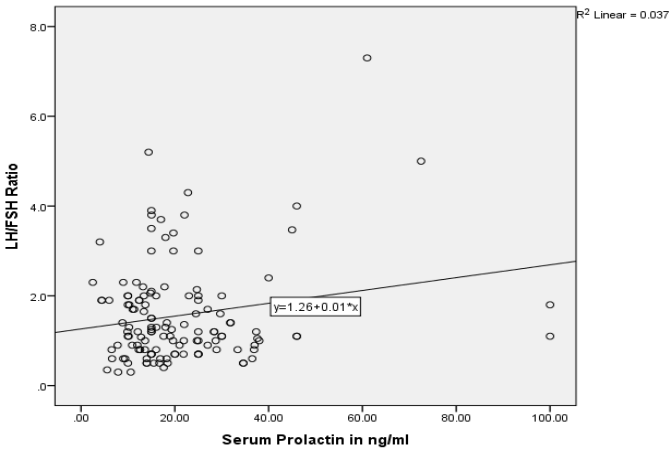

Figure 1: Correlation of LH/FSH ratio with serum prolactin level (n=130)

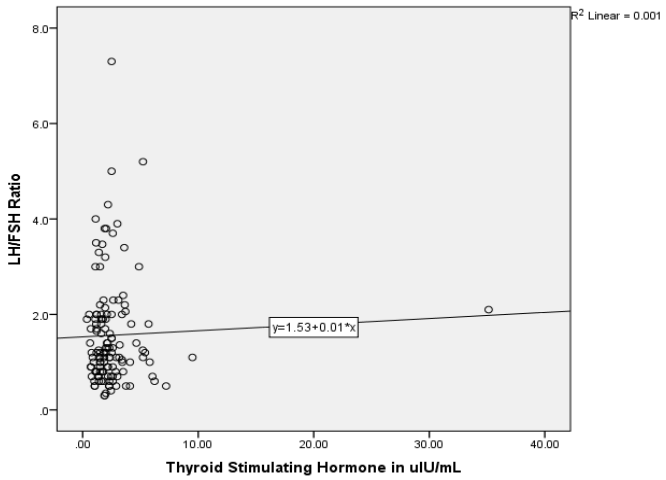

Figure 2: Correlation of LH/FSH ratio with TSH level (n=130)

irregular cycle (p-value 0.082), complications (p-value 0.072), without complications (p-value 0.550), and without comorbidities (p-value 0.645). Similarly, an insignificant mean difference of prolactin was found with menstrual regular cycle (p-value 0.750), menstrual irregular cycle (p-value 0.354), complications (p-value 0.326), comorbidities (p-value 0.132), and without comorbidities (p-value 0.281). (Table 2)

A significantly weak positive correlation of prolactin was found with LH/FSH ratio (r: 0.191, p-value 0.029). While an insignificant weak positive correlation of TSH was found with LH/FSH ratio (r: 0.037, p-value 0.679) (Figure 1,2)

DISCUSSION

The PCOS is a topic of continuous research and evolution leading to better understanding of its unrevealed pathogenesis and management options. The results our study showed 20.8% of women with LH /FSH ratio > 2. Similar results were shown in study conducted by Jesmin Et al in which 22. 3 % of women had LH/FSH ratio greater than 2.[16] While contrasting results were found in study conducted by Nath et al, they found LH /FSH ratio> 2 in 70% of women.[17] Banaszewska *et al* found LH/FSH ratio>2 in 50% of women included in the study. They also mentioned association of raised ratio with hyperinsulinemia and obesity.[18]

The most common clinical presentation in our study was menstrual irregularities which were found in 77.7% women. Study conducted by Park and colleagues found menstrual irregularities in 48.9 % of women.[19] Menstrual irregularities were also found be an important presentation in women with PCOS in study conducted by Tariq et al. in Hyderabad Sindh in which 40 % participants reported to have menstrual irregularities and irregular menstruation was reported in 60 % of women in study conducted by Sidra and colleagues.[20,21] Thus it reflects that menstrual irregularities was a significant clinical presentation in women with PCOS.

We have also observed few clinical characteristics other than menstrual irregularities including weight gain, hirsutism and infertility associated with PCOS. Thus, these factors may contribute to affect presentation of PCOS and even fertility can be affected by obesity or metabolic syndrome. This has also been reported in study by Legro et al.[22] Another study reported the association of weight gain with anovulation leading to infertility in women with PCOS.[23]

No significant association of menstrual irregularities, hirsutism, acne, infertility, weight gain, and presence or absence of polycystic ovaries was found with LH/FSH ratio in our study. A study conducted by Alnakash et al in Iraq also showed similar results.[24] However study in Bosnia revealed a positive correlation of raised LH/FSH ratio with clinical features, which showed that participants having PCOS having menstrual irregularities have raised LH/FSH ratio as compared to those having normal menstrual cycles.[25] In our study TSH was found significantly higher in PCOS women with LH/FSH > 2 as compared to LH/FSH ≤ 2. Indicating TSH as one of the factors having influence on raised LH/FSH ratio in PCOS. However, a study conducted in Iran showed no significant association was found between TSH and LH/FSH ratio.[26] Nath et al indicate TSH as an influencing factor in LH/FSH ratio in PCOS. It was mentioned that PCOS and subclinical hypothyroidism have clinical and biochemical markers of metabolic dysfunction, and both are related.[17] Kamrul-Hasan et al and Benetti-Pinto et al showed 10.8% and 11.3% of PCOS had Subchorionic Hematoma.[27]

While an insignificant mean difference of PCOS with LH/FSH was found with prolactin (p-value 0.536) which indicates that We didn't find significant association between serum prolactin and LH/FSH ratio. Similarly, Nath et al mentioned no significant correlation of LH/FSH ratio with prolactin.[17] Davoudi et al also found no association with prolactin and they mentioned increased prevalence of menstrual irregularities among PCOS having pituitary adenoma.[28] Robin et al also mentioned no association between hyperprolactinemia and PCOS and proposed to exclude causes of hyperprolactinemia.[29]

The limitations of our study are that it is a single center study and relatively smaller sample size. The clinical manifestations of hyperprolactinemia, hypothyroidism and PCOS are overlapping so on the basis of our study sample the association of these problems or independent presentation is difficult to interpret. Probably a larger sample size and multicenter involvement would give much better results. The strengths of our study are that it is discussing the association of disease entities as PCOS, hypothyroidism and hyperprolactinemia which have overlapping clinical features and need simultaneous management. It would help in the understanding of clinical features and management.

CONCLUSION

A significant correlation was found between LH/FSH ratio and TSH levels in women with PCOS which justifies the need for further evaluation. Therefore, thyroid function should be assessed in women with PCOS with

raised LH/FSH ratio which would help in management.

ETHICAL APPROVAL: The study was approved by the Institutional Review Board of a Research Study Scientific Research and Publication Committee, Liaquat College of Medicine and Dentistry , Darul Sehat Hospital Karachi (Reference Number IRB-021/LCMD/01/2018, dated: Jan 04,2019).

AUTHORS' CONTRIBUTIONS:

SAM: Concept of work, data collection analysis and interpretation of data, drafting work, critically reviewing it, approval for publication, agreed to be accountable.

FZ: Conception of work, analysis and interpretation of data, approved for publication.

FA: Data collection, analysis and interpretation of data, drafting and critically reviewing work, and final approval for publication.

SAS: Data collection, analysis and interpretation drafting the work and agreed for publication.

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