

Prolactin and thyroid stimulating hormone affecting the pattern of LH/FSH secretion in patients with polycystic ovary syndrome: A hospital-based study from North East India

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ABSTRACT

Introduction: Polycystic ovary syndrome (PCOS) is one of the most important endocrinal diseases in reproductive age group, clinically manifested by hyperandrogenism and anovulation and different other metabolic disturbances that may have important implications for long-term health. **Aim and Objective:** The aim of this study was to determine the incidence of abnormal luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio in women with polycystic ovary and to assess the influence of prolactin and thyroid-stimulating hormone (TSH) in the elevated LH/FSH ratio. **Study Design:** Retrospective observational study. **Materials and Methods:** Eighty-five women in reproductive age diagnosed with PCOS between June 2012 to June 2014 at the Department of Obstetrics and Gynecology in a tertiary care hospital were selected for the study. Serum LH and FSH levels were determined and LH/FSH ratio (normal range ≤ 2) calculated in the study subjects. They underwent a detailed clinical, hormonal, and metabolic evaluation, which was performed between the second and third days of a natural or induced menstrual period. **Results:** Elevated LH/FSH ratio was found in 60 women (70.58%). Normal gonadotropin ratio was detected in 25 women (29.41%). Statistically significant differences in serum TSH levels were noted between groups with normal and elevated LH/FSH ratio. However, no statistically significant difference was noted in other endocrine parameters. Further analysis revealed a slight negative correlation of TSH with prolactin in the study subjects of PCOS with an 'r' value of -0.3 . **Conclusions:** LH/FSH ratio is one of the characteristic attribute of PCOS women. In the present study, this abnormality was detected in 70% of patients. Hypothyroidism was a common endocrinal abnormality and prolactin was inversely correlated to TSH levels in PCOS patients.

Keywords: Luteinizing hormone/follicle-stimulating hormone ratio, polycystic ovary syndrome, prolactin, thyroid stimulating hormone

Introduction

Polycystic ovary syndrome (PCOS), also known as Stein–Leventhal syndrome, is one of the most frequent endocrine disorder among women at reproductive age and is characterized by

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infertility, hirsutism, obesity, insulin resistance, and menstrual irregularities.^[1] PCOS affects approximately 5%–10% of women in the reproductive age. In polycystic ovary syndrome, both the initial stadium of follicle growth, that is, recruitment and the growth with subsequent selection and domination proceed irregularly resulting in the accumulation of a large number of small ovarian follicles producing predominantly androgens in thecal cells, with impaired aromatization to estrogens.^[2,3]

The exact pathogenic mechanism of PCOS is unknown. There are many hypothesis concerning the causes of PCOS development and the concurrent existence of many interdependent disorders.^[4] One group of experts suggests that this disorder originates as an exaggerated adrenarche in obese girls. The combination of elevated levels of adrenal androgen and obesity leads to increased formation of extraglandular estrogen by the way of peripheral aromatization. This high amount of estrogen exerts a positive feedback on luteinizing hormone (LH) secretion and reverse in follicle-stimulating hormone (FSH) secretion resulting in a characteristic ratio of LH to FSH >2. The increased level of LH can lead to hyperplasia of ovarian stroma and theca cells causing increased androgen production that, in turn, provides more substrate for aromatization and the vicious cycle goes on.^[5,6]

Hyperprolactinemia is a condition of elevated prolactin levels in blood, which could be physiological, pathological, or idiopathic in origin. A prolactin-secreting pituitary adenoma (prolactinoma) and idiopathic hyperprolactinemia are more common in women. Other, less frequent causes are drugs, primary hypothyroidism, and non-prolactin-secreting hypothalamic or pituitary tumors that compress the pituitary stalk.^[7] Amenorrhea, galactorrhea, and infertility are the hallmarks of hyperprolactinemia in women. Hyperprolactinemia prior to menarche may results in primary amenorrhea. Hyperprolactinemia may also develop later in life leading to oligomenorrhea and ultimately to amenorrhea.^[8,9]

Hypothyroidism is caused by insufficient production of thyroid hormones by the thyroid gland. Hypothyroidism has many effects on reproductive system development and function. In women, hypothyroidism is associated with delay in the onset of puberty, anovulation, amenorrhea, polymenorrhea, menstrual irregularities, infertility, and increased frequency of spontaneous abortions. The effects of thyroid hormones on the impaired function of reproductive and to great extent is thought to be due to changes in thyroid-stimulating hormone (TSH) level, whose secretion overlaps with FSH, LH, and prolactin, and thus, it may have overlapping function.^[10,11]

Considering the intermingling clinical features of hyperprolactinemia and hypothyroidism with PCOS, the current study was undertaken with the objective of investigating the effects of prolactin and TSH in the pattern of LH/FSH secretion and also to correlate TSH secretion with prolactin in PCOS subjects.

Materials and Methods

Study design and participants

We carried out a retrospective study of patients who were admitted from June 2012 to June 2014 at the Department of Obstetrics and Gynecology, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS), which is a tertiary care hospital in Shillong, Meghalaya. The study was approved by the Institutional Ethics Committee. All the cases diagnosed as PCOS were considered and divided into two groups of LH/FSH ratio with a cut mark of 2, which is accepted as abnormal PCOS. Data collected from the records of these patients included clinical manifestations and results of laboratory tests.

PCOS was diagnosed as per European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine (ESHRE/ASRM) consensus as presence of any two of the following three criteria: (i) polycystic ovaries, (ii) oligo-/anovulation, and/or (iii) clinical or biochemical evidence of hyperandrogenism.^[12] In both groups with normal and increased LH/FSH ratio, serum insulin, prolactin, and TSH levels were determined in fasting state. These groups became the subject of a detailed clinical, hormonal analysis, which was performed between second and third day of menstrual period.

LH, FSH, free thyroxine levels (free T3 and free T4), TSH, and prolactin were measured by specific chemiluminescence assays (Beckman coulter Access 2 immunoassay system). Under aseptic and antiseptic precaution, 3 mL of fasting blood sample was collected by venipuncture. Collected samples were allowed to clot completely in stoppered tube before centrifugation. Within half the hours after centrifugation, at least 500 μ L of cell-free sample was transferred to sample cup and processed immediately. All the parameters were processed only after successful calibration. Strict quality control was maintained using Bio-Rad Lyphochek immunoassay plus control as an internal quality control material.

Statistical analysis

Sample size calculation was done by *n* master. Statistical analysis was done using *t*-test. A null hypothesis was created with acceptable α of 5% and power of study maintained at 80% with two-tailed distribution. Differences at $P < 0.05$ were considered statistically significant. SPSS data editor and Microsoft office excel 2007 were used to calculate the data.

Results

Elevated LH/FSH ratio (LH/FSH > 2) was found in 70.58% of the studied PCOS women (60 out of 85), whereas gonadotropin ratio was normal in 29.41% studied cases (25 out of total 85) [Figure 1]. Mean and standard deviation of all the parameters were calculated and represented in Figure 2 using cut mark of LH/FSH ratio of 2. Statistically significant differences were noted between groups with normal and elevated

LH/FSH ratio in the serum TSH [Figure 3]. However, no statistically significant difference was noted in other endocrine parameter [Table 1]. A slight negative correlation of TSH with prolactin in the study subjects of PCOS with an 'r' value of -0.3 [Figure 4] has been noted.

High prolactin levels were found in 28 patients. Of 28 patients with high prolactin level, 7 (25%) had regular periods and 21 (75%) had irregular periods [Table 2]. Oligomenorrhea (33.3%) was the most common menstrual disorder followed by amenorrhea (23.8%) and polymenorrhea (23.8%) and hypomenorrhea (19%). Patients with menstrual irregularities had higher prolactin levels (59.29 ± 12.02) as compared with those with normal menstrual cycle (30.64 ± 2.64), although there was no correlation between the different pattern of menstrual irregularities and prolactin levels [Table 3].

Discussion

PCOS is a subject of continuous research in view of new insights in the pathogenesis and therapeutic approach. The

overproduction of LH due to hypothalamic-pituitary ovarian or adrenal axis dysfunction leading to disturbance in the pulsatility of gonadotropin-releasing hormone (GnRH) and consequently the incorrect LH/FSH ratio is considered to be a characteristic attribute of all PCOS patients.^[13,14] An abnormal feedback mechanism by ovarian estrogen is blamed to play role in this discriminated increase in LH release. Insufficient levels of FSH leads to impaired follicular development, while increased levels of LH leads to increase ovarian androgen production.^[15] As a result of this derangement, the ratio between FSH and LH levels, which is normally around 2:1, become reversed and sometimes even more (2 or 3 to 1) in approximately 60% of the patients with PCOS, which agree with the results obtained in this study where about two-third of the women with PCOS have high LH/FSH ratio (LH/FSH ratio >2 in 70%). In the recent literature, attention has been focused on insulin resistance and hyperinsulinemia in the development of PCOS and it has been stated that prevalence of hyperinsulinemia may be as high as 40%–60% in patients with PCOS.^[16-19]

Banaszewska *et al.* reported abnormal LH/FSH ratio when it is >2 and 45.4% of PCOS women having an elevated ratio; furthermore, they found that most of PCOS women with normal LH/FSH ratio belong to a subgroup of patients with hyperinsulinemia and obesity and patients with hyperinsulinemia and excess of LH constitute probably a separate subpopulation with increased adrenal androgenic activity.^[4]

On the other hand, Cho *et al.* found that LH/FSH ratio has little use in diagnosing PCOS because the median LH/FSH ratio did

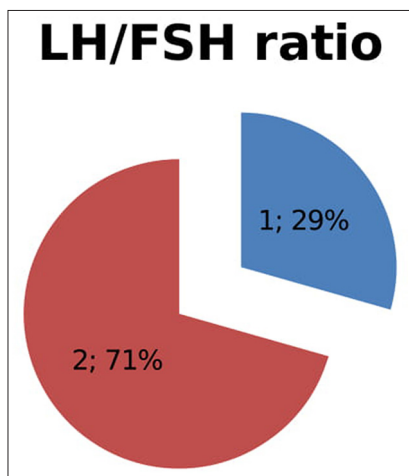


Figure 1: Luteinizing hormone/follicle-stimulating hormone ratio in the study group

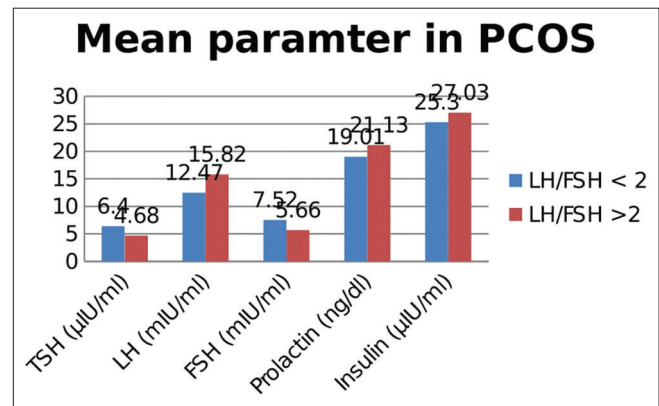


Figure 2: Mean of different parameters in the study group

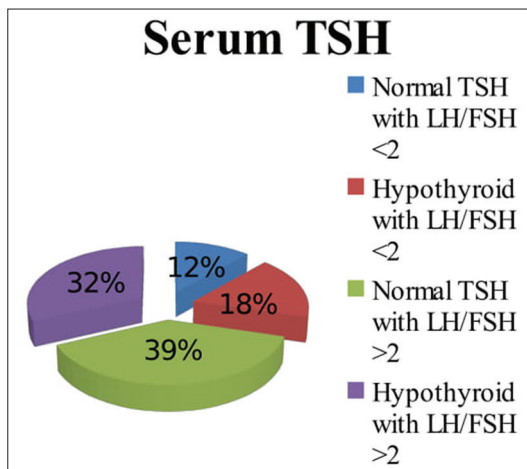


Figure 3: Thyroid hormone status in the study group

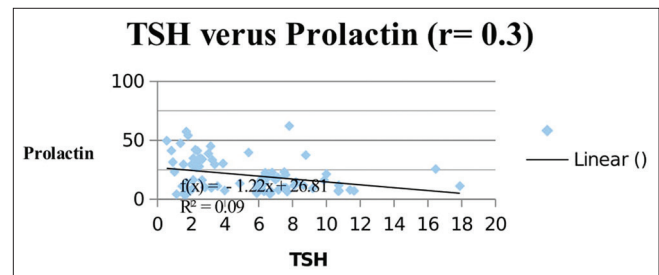


Figure 4: Correlation of thyroid-stimulating hormone and prolactin in the study group

not differ significantly between the PCOS and non-affected group.^[20]

Prolactin excess associated with low levels of LH and FSH and constitutes a specific subtype of hypogonadotropic hypogonadism. It is found that one-tenth or more of amenorrhic women have increased levels of prolactin, and more than half of women with both galactorrhea and amenorrhea have been found to be elevated prolactin levels. In our study, no significant differences in prolactin secretion were noted in relation with the study groups [Table 1]. This may be due to the fact that prolactin inhibits reproductive function by suppressing hypothalamic GnRH and pituitary gonadotropin secretion and by impairing gonadal steroidogenesis in both women and men. In the ovary, prolactin blocks folliculogenesis and inhibits granulosa cell aromatase activity, leading to hypoestrogenism and anovulation.^[21,22]

Also, we observed a high frequency of menstrual disorders (around 75%) in patients with hyperprolactinemia. In this study, around 33% and 24% of patients with hyperprolactinemia had oligomenorrhea and amenorrhea, respectively. Kulshreshtha *et al.* in his review of 128 females with hyperprolactinemia reported oligomenorrhea and amenorrhea in 44% and 35% of patients, respectively.^[23] Berinder *et al.* in a study on 271 women with hyperprolactinemia (71% of whom had prolactinomas) observed that 26% had oligomenorrhea and 61% had amenorrhea.^[24] Touraine *et al.* similarly observed in their cohort of 122 patients with prolactinoma that around 66% patients had amenorrhea and 26% had oligomenorrhea.^[25] The frequency of amenorrhea was much higher in these two studies compared with our study.

In this study, it was noted that 56% of the total test subjects had the evidence of hypothyroidism (cut off value 5.64 µIU/mL) [Figure 3]. There is statistically significant difference in the mean value of test groups with LH/FSH <2 and LH/FSH >2 with a ‘P’ value of < 0.05 [Table 1]. This indicates that TSH is one of the influencing factors in the LH/FSH ratio in PCOS. Interestingly, our study has showed a slight negative correlation of TSH with prolactin in the study subjects of PCOS with an ‘r’ value of -0.3 [Figure 4]. Though it is difficult to fully explain these results, but we may only speculate due to the fact that iodine deficiency remains the most common cause of hypothyroidism worldwide. It is prevalent in many mountainous regions like our location. The World Health Organization estimates that about 2 billion people are iodine-deficient based on urinary excretion data. Despite iodine supplementation of salt, bread, and other food substances, iodine deficiency remains the most common cause of preventable mental deficiency. Studies have showed that long standing hypothyroidism leads to an increase in ovarian volume, which can also be accompanied by cyst formation. Literature also shows that thyrotropin-releasing hormone is a potent stimulus of prolactin and the association between hypothyroidism and hyperprolactinemia is well appreciated.^[26]

Since all these endocrinological manifestation of hypothyroidism and hyperprolactinemia may lead to the development of PCOS and clinical manifestations are intermingled, it is very difficult to comment in our study whether these conditions are interdependent or presented with separate entity.

Primary care physician who are at the frontline of healthcare delivery system can improve the patient-provider relationship by tailoring their advice to acknowledge the broad impact that PCOS has on women’s lives. Studies have shown a substantial lag period between symptom onset and diagnosis of PCOS by multiple healthcare providers.^[27] It is important to strengthen the healthcare system by improving awareness regarding social burden of PCOS among women and health professionals to improve timely diagnosis and look after different endocrinology parameters at the primary care level.

Conclusion

PCOS is a very heterogeneous disorder with intermingling pathogenesis and clinical features. The traditional concept of high LH/FSH ratio with PCOS is still significant and may add more to the disease mystery. Assessment of thyroid status and prolactin should be carried out in all patients with PCOS in addition to other hormonal assays like LH and FSH.

Table 1: Different endocrine parameters in the study group

| Parameter | PCOS with LH/FSH <2 n=25 | PCOS with LH/FSH >2 n=60 | P |
|-------------------|--------------------------|--------------------------|-------|
| TSH (µIU/mL) | 6.40±4.22 | 4.68±3.09 | <0.05 |
| Prolactin (ng/dL) | 19.01±14.28 | 21.13±14.16 | NS |
| Insulin (µIU/mL) | 25.30±8.91 | 27.03±9.74 | NS |

PCOS: Polycystic ovary syndrome; LH/FSH: Luteinizing hormone/follicle-stimulating hormone; TSH: Thyroid-stimulating hormone

Table 2: Comparison of prolactin in menstrual cycle

| Menstrual history | Mean | SD | SEM | Mean difference | 95% CI | P (two-tailed unpaired t-test) |
|-------------------|-------|-------|-------|-----------------|------------|--------------------------------|
| Normal (n=7) | 30.64 | 2.64 | 0.996 | | | |
| Abnormal (n=21) | 59.29 | 12.02 | 2.62 | 28.64 | 22.86-34.4 | 0.000 |

Table 3: Comparison of prolactin in subgroups of abnormal menstrual cycle

| Menstrual history | Mean | SD | SEM | Mean difference | 95% CI | P (two-tailed unpaired t-test) |
|----------------------|-------|-------|------|-----------------|----------------|--------------------------------|
| Oligomenorrhea (n=7) | 52.78 | 14.8 | 5.59 | | | |
| Amenorrhea (n=5) | 62.77 | 8.13 | 3.63 | 9.98 | -26.38 to 6.41 | 0.205 |
| Polymenorrhea (n=5) | 58.97 | 10.31 | 4.61 | 6.19 | -23.4 to 11.02 | 0.44 |
| Hypomenorrhea (n=4) | 66.72 | 10.11 | 5.05 | 13.93 | 32.9 to 5.09 | 0.132 |

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Conflicts of interest

There are no conflicts of interest.

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