Original Article

Pattern of Common Hormonal Disorders among Patients with Polycystic Ovarian Syndrome at a Tertiary Health Facility in Nigeria

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Abstract

Background: Polycystic ovarian syndrome (PCOS) is a disease associated with multiple reproductive and metabolic endocrine disorders. It is associated with cardiometabolic complications with established morbidity and mortality. **Aim:** We studied the pattern of these endocrine disorders associated with PCOS will aid the understanding of the pathophysiology of this relatively incompletely understood syndrome, particularly among Africans. **Patients, Materials and Methods:** One hundred adult females aged between 18 and 44 years, who were newly diagnosed with PCOS, and 100 age-matched non-PCOS women were involved in the study. Their serum samples were analyzed for follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, progesterone, estradiol, testosterone, leptin, and anti-Mullerian hormone (AMH) using ELISA method. **Results:** The mean age of the test subjects in this study was 26.4 ± 6.0 years versus 33.3 ± 6.6 years in controls. The mean weights and body mass index of the test subjects and controls were 89.1 ± 13.9 kg versus 64.7 ± 11.3 kg, $P = 0.04$, and 34.01 ± 3.5 kg/m^2 versus 23.8 ± 3.9 kg/m^2, $P = 0.034$, respectively. The mean serum LH was significantly higher among subjects than that of controls (11.4 ± 7.4 vs. 5.7 ± 4.8 mIU/mL, $P = 0.001$); similarly the mean serum LH: FSH ratio was significantly higher among subjects and controls in this study (1.9 ± 1.1 vs. 1.1 ± 0.8, $P = 0.042$). Serum AMH, insulin, leptin, and testosterone levels were higher among subjects than controls (7.5 ± 5.4 vs. 2.7 ± 0.4 ng/mL, $P = 0.001$, 21.6 ± 7.3 vs. 18.0 ± 3.01 µIU/mL, $P = 0.004$, and 18.6 ± 4.0 vs. 3.5 ± 1.5 ng/mL, $P = 0.003$, 1.0 ± 0.2 vs. 0.6 ± 0.2 ng/mL, $P = 0.042$, respectively). Mean serum prolactin was significantly higher among subjects when compared to controls. The prevalence of hyperinsulinemia, hyperleptinemia, and hyperandrogenemia among subjects in this study was higher when compared to controls. **Conclusion:** PCOS is a disease of multiple and inter-related endocrine disorders; a study of the frequencies and distributions of these associated disorders can aid the understanding of the pathophysiology of the disease particularly among Africans where limited studies have been carried out.

Keywords: Distributions, frequencies, hormones, polycystic ovarian syndrome

Introduction

According to the 2003 Rotterdam consensus workshop, polycystic ovarian syndrome (PCOS) is a constellation of ovarian dysfunction along with the cardinal features of hyperandrogenism and appearance of polycystic ovary.[1] It still remains a disease of unknown etiology with associated long-term medical complications, including cardiac risks and Type 2 diabetes mellitus.

PCOS is a disease associated with multiple reproductive and metabolic endocrine disorders.[2] It has been described as a functional hyperandrogenic disorder as a result of excess serum androgens and its clinical features such as acne, hirsutism, virilization, and reproductive dysfunction.[3] The androgens include testosterone, dehydroepiandrosterone (DHEA),

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DHEA-S, and androstenedione. Androgen excess is a common feature of PCOS, which is also the most common cause of anovulatory infertility.[3] The suggested mechanism of hyperandrogenism in PCOS involves ovarian theca cell synthesis of androgens under the stimulatory activity of the raised luteinizing hormone (LH) levels, and, in many cases, raised insulin levels. PCOS is also associated with hyperinsulinemia from insulin resistance, resulting in impaired glucose tolerance. In addition, serum sex hormone binding globulin level, which normally binds 62%–78% of female androgens, is reduced among PCOS patients, leading to increase in the free fractions of androgens and associated clinical features.[4]

Anti-Mullerian hormone (AMH), a member of the transforming growth factor beta superfamily, is another hormone implicated in the etiopathogenesis of PCOS.[5] AMH is produced normally in the granulosa cells of pre-antral and small antral follicles in females. As these follicles are usually increased in the ovaries of patients with PCOS, corresponding increase in AMH has been found in the same group of patients. The increased serum AMH level is independent of the patients' body mass index (BMI), adiposity, and degree of insulin resistance.[5,6] Serum AMH level however correlates not only with androgens and LH rise, but also more importantly with the severity of ovarian findings on ultrasonography in patients with PCOS.[7]

The ratio of LH to follicle-stimulating hormone (FSH) in PCOS is usually greater than 2:1 and can be as high as 4.6–5.5:1.[8] This increase in LH/FSH ratio results from increase in hypothalamic gonadotropin-releasing hormone (GnRH) pulsatile release frequency, while the pulsatile GnRH release is believed to be due to hyperinsulinemia.[9] Hyperinsulinemia appears to be the common denominator of all other associated endocrine abnormalities found in PCOS.[9]

The role of hyperprolactinemia in PCOS has been attributed to a common origin of hypothalamo–pituitary axis in both conditions. Studies have shown synchronization between serum prolactin and LH peaks among patients with PCOS.[10]

PCOS is the most common endocrine disorder among women globally.[11] It affects between 2% and 20% of women aged between 18 and 44 years and yet the disease is still not fully understood.[12] The prevalence of PCOS among infertile women in Nigeria ranges between 12.2% and 18.1%.[13,14] It is associated with the risk of developing serious medical complications such as obesity, Type 2 diabetes mellitus, and coronary artery disease. Hyperleptinemia is associated with a majority of these conditions and therefore proposed to also have a role in PCOS.[15] These complications are individually and collectively the causes of increasing morbidity and mortality.[16]

PCOS is also one of the causes of female infertility and menstrual irregularities, causing strains on marital union and anxiety among patients.[17] Assessing the prevalence and distribution of some of these hormonal abnormalities among individuals with PCOS will aid the understanding of the pathophysiology and management of this disease.

This study aims to evaluate the prevalence, distribution, and frequency of some hormonal disorders associated with PCOS at Federal Medical Centre, Abeokuta, Ogun State, Southwestern Nigeria, through assay of serum fasting insulin, LH: FSH ratio, serum AMH, serum testosterone, serum leptin, and serum prolactin levels among patients with PCOS.

Patients, Materials and Methods

Ethical approval for this study was obtained from the Ethical Research Committee, Federal Medical Centre, Abeokuta. The study was conducted at the Department of Obstetrics and Gynaecology and the Department of Chemical Pathology, Federal Medical Centre, Abeokuta, Southwestern Nigeria. The hospital receives referrals of patients with infertility and suspected cases of PCOS from Ogun State and other neighboring states. The hospital runs gynecological and infertility clinics three days/week.

It is a cross-sectional analytical study of consecutive patients with PCOS who met the inclusion criteria and non-PCOS controls. Sampling was conducted using the convenient recruitment method. The duration of study was from March 2020 to February 2021. Included in this study were females between aged between 18 and 44 years with at least two of the following three Rotterdam consensus criteria:

a. Clinical and/or biochemical hyperandrogenism
b. Menstrual disorders
c. Polycystic ovaries.

The following categories of females were excluded from this study:

- Known PCOS patients on treatment, pregnant women, breastfeeding women, patients on hormonal replacement therapy, women on contraceptives, those with diabetes mellitus, and those with hormonal disorders such as hyperprolactinemia and thyroid disorders.

The study population included 100 adult females aged between 18 and 44 years, who are newly diagnosed with PCOS, based on the 2003 Rotterdam consensus criteria. Another 100 age-matched, apparently healthy females, with no biochemical, clinical, and ultrasonographic evidence of PCOS, served as controls.

Samples were obtained on day three of the menstrual cycles for FSH, LH, prolactin, testosterone, estradiol, leptin, AMH, and insulin, whereas serum progesterone sample only was obtained on day 21 of the menstrual cycle. Patients were asked to fast 10–12 h overnight for sample collection. 5 mL of blood was collected from the patients in plain vacutainer tubes. The samples were allowed to clot and then centrifuged for 20 min at 3000 rpm. Serum samples were separated and stored at −20°C till the required sample numbers are obtained. Then, the samples were analyzed for insulin, FSH, LH, prolactin, testosterone, estradiol, progesterone (day 21), and AMH, using Calbiotech ELISA kits.

The reference intervals for the assayed hormones, as stated in the kit manuals, are as follows:

FSH: 1.37–9.9 mU/mL, LH: 1.68–15.0 mU/mL, prolactin 1.2–19.5 ng/mL, testosterone: 0.2–0.95 ng/mL, leptin: 3.3–18.3 ng/mL, insulin: fasting <25 mU/L, AMH: 1.0–4.0 ng/mL, estradiol: 20–350 pg/mL, and progesterone: 2.0–25.0 ng/mL.

Polycystic ovaries were established when at least one ovary demonstrated an ovarian volume of greater than 10 mL or 12 or more follicles measuring 2–9 mm in diameter on ultrasonography.

Statistical analysis

Statistical analysis was done with the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA). Normally distributed data were expressed as mean ± SD, while parameters displaying $P < 0.05$ were considered statistically significant.

Results

The mean age of the subjects in this study was 26.4 ± 6.0 years versus 33.3 ± 6.6 years in the controls. The mean weights and BMIs of the test subjects and controls were 89.1 ± 13.9 kg versus 64.7 ± 11.3 kg, $P = 0.04$, and 34.01 ± 3.5 kg/m^2 versus 23.8 ± 3.9 kg/m^2, $P = 0.034$, respectively. The mean serum LH was significantly higher among subjects than controls (11.4 ± 7.4 vs. 5.7 ± 4.8 mIU/mL, $P = 0.001$), so also was the mean serum LH: FSH ratio among the subjects and controls in this study (1.9 ± 1.1 vs. 1.1 ± 0.8, $P = 0.042$) [Table 1]. There was no statistically significant difference between the mean serum FSH levels in subjects and controls (6.8 ± 5.5 vs. 5.8 ± 2.8, $P = 0.331$).

There were significantly higher serum AMH, insulin, leptin, and testosterone levels among subjects than controls (7.5 ± 5.4 vs. 2.7 ± 0.4 ng/mL, $P = 0.001$, 21.6 ± 7.3 vs. 18.0 ± 3.01 µIU/mL, $P = 0.004$, and 18.6 ± 4.0 vs. 3.5 ± 1.5 ng/mL, $P = 0.003$, and 1.0 ± 0.2 vs. 0.6 ± 0.2 ng/mL, $P = 0.042$, respectively). The mean serum prolactin was significantly higher among subjects compared to controls [Table 1].

However, the mean serum values of progesterone and estradiol were significantly lower among subjects when compared with controls (1.8 ± 1.7 vs. 13.0 ± 5.4 ng/mL, $P = 0.001$, 130.9 ± 97.0 vs. 261.3 ± 75.9 pg/mL, $P = 0.001$, respectively) [Table 1].

The prevalence of hyperinsulinemia, hyperleptinemia, and hyperandrogenemia among subjects and controls in this study was 15.8% versus 2.6%, 26.3% versus 2.6%, and 36.7% versus 0%, respectively. The LH: FSH ratio was ≥2 in 86.5% of subjects compared to 44.7% in the controls. Approximately 15.8% of PCOS patients were hyperprolactinemic compared to 10.3% among controls [Figure 1].

Discussion

The mean age of the subjects in this study was lower than the mean age of the controls (26.4 ± 6.0 years vs. 33.3 ± 6.6 years in controls, respectively). This is consistent with the findings in a similar study that showed females of lower reproductive age group presenting more with

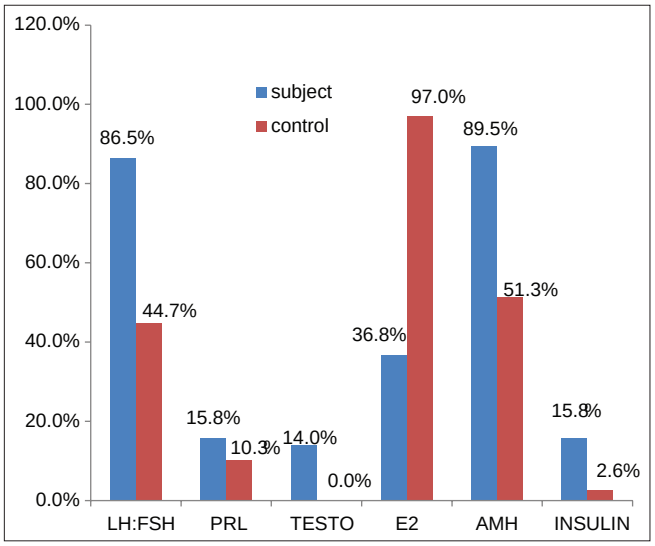

Figure 1: Comparison of prevalence of hormonal disorders among subjects and controls

Table 1: Comparison of mean serum concentration of selected hormones among subjects and controls

	Subject (mean±SD)	Control (mean±SD)	*P*
Age (years)	14-41 (26.4±6.0)	14-43 (33.3±6.6)	0.001
LH (mIU/mL)	1.92-33.6 (11.4±7.4)	0.86-19.52 (5.7±4.8)	0.001
FSH (mIU/mL)	0.6-31.5 (6.8±5.5)	0.9-12.3 (5.8±2.8)	0.331
LH: FSH	0.23-4.8 (2.9±1.1)	0.11-3.6 (1.1±0.8)	0.042
Progesterone (ng/mL)	0.1-11.2 (1.8±1.7)	3.2-29.7 (13.0±5.4)	0.001
Estradiol (pg/mL)	9.2-294.6 (130.9±96.5)	117.7-546.9 (261.3±75.9)	0.001
AMH (ng/mL)	0.5-17.2 (7.5±5.4)	0.4-13.5 (2.74±0.4)	0.001
Insulin (µIU/mL)	2.75-53.8 (21.6±7.3)	13.0-28 (18.1±3.0)	0.004
Prolactin (ng/mL)	0.16-104 (18.4±3.9)	4.54-11.9 (9.4±2.9)	0.048
Leptin (ng/mL)	1.06-114.12 (18.6±4.0)	0.66-58.66 (3.5±1.5)	0.003
Testosterone (ng/mL)	0.1-2.9 (1.0±0.2)	0.12-1.1 (0.6±0.2)	0.042

P<0.05 statistically significant. FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, SD: Standard deviation, AMH: Anti-Mullerian hormone

PCOS (26.9 ± 4.6 vs. 29.9 ± 5.9 years; $P = 0.12$)[18] and mean age of 30.0 + 5.2 years (range: 17–41 years) obtained in a similar study in South-eastern Nigeria.[14]

The mean serum LH and mean serum LH: FSH ratio ≥2 were significantly higher among PCOS patients when compared to non-PCOS controls. This is similar to findings in some studies,[16,17] and has been shown to be a valuable tool in the assessment of suspected PCOS patients, with good sensitivity, specificity, and accuracy when LH: FSH >1 was utilized.[19,20] It has also been proposed as a diagnostic criterion.[19] However, some other studies have shown that it has limited sensitivity or no value at all in the evaluation of women with oligo/amenorrhea to rule out PCOS, though these studies used very low number of subjects and LH: FSH >3 as their cutoff point.[21,22] This inappropriate gonadotropins release (high serum LH and low/normal serum FSH) was found to be related to the increase in total ovarian volume and antral follicle count (AFC), two characteristic ultrasonographic findings in PCOS, which were found to be inversely related to BMI in a study.[23,24]

The mean serum AMH level was higher among PCOS patients when compared to non-PCOS controls in this study, which is consistent with increase in AFC and increase in AMH production per follicle in PCOS, as suggested by numerous other studies.[25,26]

Hyperandrogenism is regarded as the biochemical hallmark of PCOS.[27] Nearly 36.7% of subjects in this study had elevated serum testosterone levels. Although elevated serum testosterone is not a mandatory criterion for diagnosis of PCOS, perhaps the percentage of subjects with hyperandrogenemia might have been higher if other androgens such as DHEA, DHEAS, and androstenedione were also assayed. The disruption of the feedback control of the hypothalamo–pituitaro–ovarian axis (HPOA), which leads to increased pulsatile release of GnRH and LH, causing increased testosterone secretion by the ovarian theca cells, has been suggested as the mechanism of hyperandrogenemia in PCOS. Hyperandrogenemia, by further disrupting the gonadic feedback on the HPOA, leads to more increase in GnRH and LH and hence the disruption becomes a cascade.[28-30]

Hyperinsulinemia or insulin resistance is essential in the pathophysiology of PCOS.[31] The mean serum insulin is significantly higher among subjects in this study when compared to non-PCOS controls and with hyperinsulinemic prevalence of 15.8%. The suggested mechanism of hyperinsulinemia in PCOS patients is postreceptor defects in the insulin receptor signal transduction, through upregulation of insulin receptor serine phosphorylation, causing a decrease in its protein kinase and hence, insulin resistance or a reduction in insulin clearance due to receptor defect insulin and insulin-like growth factor-I receptors is found in normal and polycystic ovaries and found to play a significant role in ovarian steroidogenesis.[32-34] This role is preserved and enhanced in PCOS despite insulin resistance.[35] Hyperinsulinemia is also intrinsically linked to hyperandrogenemia in PCOS. Elevated insulin is said to have co-gonadotropin effects on the ovarian theca cells, to enhance androgen synthesis, functioning as both a metabolic and reproductive hormone and also amplifies the effects of GnRH agonist on ovarian steroidogenesis in women with PCOS.[33,36] In a bi-directional relationship, androgens have also been implicated as a causative factor of hyperinsulinemia through raising serum levels of free and storage forms of fatty acids and enhancing adiposity.[37-39]

Hyperleptinemia role in the pathophysiology of PCOS is multidimensional. It has been suggested that its roles in PCOS cut across the entire HPOA. By suppressing neuropeptide Y, which inhibits GnRH secretion, hyperleptinemia causes increased GnRH and subsequently increased LH secretion; both conditions have been implicated in the pathogenesis of PCOS.[40] Leptin also has direct effects on follicullogenesis and promotes steroidogenesis, while hyperleptinemia causes arrest of follicular development.[41,42]

PCOS and hyperprolactinemia are known as the two most common causes of anovulation in women of childbearing age.[43] Hyperprolactinemic prevalence of 15.8% obtained in our study is similar to 16% obtained in a similar study.[44] Various mechanisms have been suggested for hyperprolactinemia in PCOS including synchronization of LH and prolactin peaks and effects of hyperestrogenemia, similar to the findings in this study.[45] Hyperprolactinemia may also be associated with hyperinsulinemia by increasing adiposity and by causing insulin receptor defects.[46]

PCOS is evidently a disease of multiple endocrinopathies: hyperandrogenemia, hyperleptinemia, hyperinsulinemia, elevated AMH, and hyperprolactinemia. An understanding of the relationship between these different hormones in the pathophysiology of PCOS will aid the diagnosis and management of PCOS and its associated complications such as diabetes mellitus, infertility, obesity, cardiovascular diseases, and metabolic syndrome.

Limitation of study

Our study is limited by the convenience sampling method, hence our findings may not be generalized but applicable mainly to the study population.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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