Niger. J. Physiol. Sci. 40 (June 2025): 41 – 47
www.njps.physiologicalsociety.com

Niger. J. Physiol. Sci.

Full-length Research Article

Characterization of the Clinical Phenotype and Reproductive Hormones of Polycystic Ovary Syndrome in Nigerian Population

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Summary: This study described the peculiarity of the clinical phenotypes and the pattern of reproductive hormones among women with Polycystic Ovary Syndrome (PCOS) in the Nigerian populace. A total of 90 consented volunteers consisting of 45 PCOS and 45 controls were recruited. The diagnosis of PCOS was established using the International PCOS guidelines 2018. Demographic, anthropometric, and clinicopathological data were obtained from each participant. Hormonal assay was done using the electrochemiluminescence (ECL) technology (Roche Diagnostics, Switzerland). Statistical analysis was done using the statistical package for the social sciences (SPSS) version 25. Polycystic ovaries (PCO) are the most popular feature of PCOS, observed in more than 90% of PCOS subjects, followed by oligomenorrhea (68 %), while hirsutism and acne were found in about 50% of the cases. The study shows 62 % of PCOS subjects had phenotype D, 52 % Phenotype C, 40 % Phenotype B, while 38 % had Phenotype A. Increased levels of Anti-Mullerian hormone (AMH), Testosterone, Prolactin, Luteinizing hormone (LH) and LH: FSH were observed in PCOS with median (95% Confidence interval) of 4.98(3.4-7.1), 32.5(19.75-53.0), 401.6(230.9-623.0), 9.23(5.4-16.6) and 2.03(1.48-3.58), respectively compared to control [1.43(0.8-2.4), 19.0(12.3-29.5), 252.2(196.3-337.0), 6.36(4.0-12.6) and 1.47(0.7-2.4), respectively] ($p<0.05$). The serum levels of follicle-stimulating hormone (FSH), estradiol, and sex hormone binding globulin (SHBG) were lower in PCOS with values of 5.21(3.6-5.9), 70.45(50.5-145.9) and 44.84(27.3-75.7), respectively compared to controls [6.0(4.4-7.9), 104.0(64.6-216.6) and 74.05(54.0-96.8), respectively] ($P<0.05$). FSH, LH:FSH, AMH, testosterone, estradiol, SHBG, and prolactin show significant odd ratio with risk analysis in PCOS ($p<0.05$). There existed a negative correlation between the hormones (Estradiol and AMH) and the PCOS phenotypes (estimated Spearman's rho were -.310 and -.348, respectively) ($p<0.05$). Phenotype D and C characterized by ovulatory dysfunction, polycystic ovary morphology and hyperandrogenism are the two predominant phenotypes of PCOS in our study population. This is accompanied by marked changes in hormonal pattern among PCOS subjects, particularly steroids and follicular hormones. Modulating this phenotype-hormonal interplay may support or improve PCOS management in the study population.

Keywords: *Polycystic Ovarian Syndrome, Reproductive Hormones, Clinical Phenotype.*

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Manuscript received: March 2015; Accepted: May 2025

DOI: https://doi.org/10.54548/njps.v40i1.5

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a group of symptoms associated with endocrine disorders and has been described as the main endocrine disorder in women, with an associated increased risk for infertility and a myriad of metabolic conditions (Conway *et al*., 2014). The global prevalence of PCOS has been reported to range from 6% to 10% (Bozdag, 2016). Different diagnostic criteria are believed to have contributed to the variation in the prevalence of PCOS reported across various populations.

The diagnosis of PCOS depends on clinical, morphological, and biochemical criteria. Stein and Leventhal first described polycystic ovaries by linking ovulatory dysfunction with morphologic changes of the ovaries to define the PCOS (Stein and Leventhal) Since 2003, a threshold of 12 follicles (measuring 2–9 mm in diameter) per whole ovary has been largely used, which now seems outdated. Under Rotterdam criteria, PCO morphology is defined as a follicle number per ovary of ≥ 12 and/or an ovarian volume of >10 cc in at least one ovary, however, the 2014 Androgen Excess and PCOS Society task force recommended the use of ≥25 follicles and/or a

volume of >10 cc (Dewailly, *et al*., 2014), and in a more recent data, the International PCOS Guideline for diagnosis of PCOS revised the criteria for definition of PCO morphology and thus, recommended ≥20 antral follicles (2-9 mm) per ovary and/or an ovarian volume ≥10 mL as a diagnostic threshold using a transducer frequency ≥8 MHz (Teede, *et al*., 2018). Four phenotypic classifications of PCOS have been recommended as follows: Phenotype A: Hyperandrogenism (HA) (clinical or biochemical presence) + Ovulatory Dysfunction (OD) + Polycystic Ovary (PCO) morphology; Phenotype B: HA + OD; Phenotype C: HA + PCO; and Phenotype D: OD + PCO (Teede, *et al*., 2018).

The most common clinical symptoms of PCOS include menstrual disorders such as oligomenorrhea or amenorrhea, infertility, high levels of masculinizing hormones manifested by acne and hirsutism, and metabolic syndrome which appear as a tendency towards central obesity and other symptoms associated with insulin resistance [Kabel, 2016]. Available data on PCOS pathophysiology suggests the role of different factors, including androgen excess, obesity, insulin resistance, environmental factors, genetic, and epigenetics (Adewuni *et al*, 2022, Bednarska and Siejka 2017, Ganie *et al*., 2019). The hypothalamic-pituitary unit and the ovaries feedback communication is an important component of the woman reproductive cycle, and estradiol and progesterone play a major role in these feedback communications. Women with PCOS experience an increase in hypothalamic Gonadotropin-releasing hormone pulses frequency and this result in an increased LH/FSH ratio (Lewandowski *et al*., 2011) In women, pituitary gonadotropins regulate oocyte development, folliculogenesis, and the development and maintenance of the corpus luteum. Follicle-stimulating hormone (FSH) and Luteinizing hormone (LH) drive the synthesis of the traditional gonadal sex steroid hormones: estradiol from granulosa cells, androstenedione from theca cells, and progesterone from luteinized granulosa cells (Garg and Berga, 2020)

The heterogeneity of PCOS may well reflect multiple pathophysiological mechanisms, however, the exact etiology and pathogenesis, especially in our study population have not been well-established.

MATERIALS AND METHODS

Study Population: The study involved a total of 90 consented volunteers (50 PCOS and 40 controls). PCOS diagnosis was done using the criteria defined by International PCOS guidelines 2018, requiring the presence of any two of (1) Oligomenorrhea – and/or anovulation, (2) Clinical and/or biochemical signs of hyperandrogenism, and (3) Polycystic ovary morphology (presence of 12 or more follicles in each ovary, 2-9 mm in diameter and/or increased ovarian volume>10mL). Apparently, healthy age-matched women with no PCOS were recruited as controls.

Ethical Approval: Ethical approval was granted by the Health Research Ethics Committee, Lagos State Ministry of Health Service Commission (No. LSHSC/2222/VOL.I/64).

Demographic and Clinical Data: General demographic and clinicopathological details were obtained from the participants using structured questionnaires. Anthropometric data such as height, weight, waist circumference, and hip circumference were measured by conventional methods, and the body mass index (BMI) was calculated as weight (kg)/height^2 (m2), while the waist-hip ratio (WHR) was calculated as the measurements of the waistline/hipline ratio.

Sampling and Hormonal Assay: Five mL of venous blood was collected into plain bottle and centrifuged for 10 mins at 3000rpm to separate serum for hormonal analysis. LH, FSH, AMH, Testosterone, Progesterone, Estradiol, Dehydroepiandrosterone sulfate (DHEAS), SHBG and Prolactin were assayed using electrochemiluminescence (ECL) technology (Roche Diagnostics, Switzerland).

Statistical analysis: Statistical data analysis was performed using IBM SPSS version 25 (IBM Illinois, USA). Data were analyzed using student's t-test, Mann-Whitney U, ANOVA and Logistic regression, where appropriate. A p-value < 0.05 was considered statistically significant. The calculated sample size was 37, however, to increase the power of the study, the actual PCOS sample size used was 50.

RESULTS

The demographic and anthropometric characteristics of the PCOS and controls were presented in Table 1. The mean weight, BMI, waist circumference, and waist-hip ratio were higher in PCOS (77.70±15.7, 29.57±6.0, 0.93±0.1 and 0.87±0.1, respectively) compared to the controls (68.43±11.5, 26.19±4.4, 0.87±0.1 and 0.83±0.1, respectively) p<0.05. Figure 1 shows the clinical characteristics distribution among the study population. 58 % had hirsutism, 94 % showed polycystic ovaries (PCO) morphology on Transvaginal scan, 68 % had Oligo/amenorrhea, 46 % had acne, and 8 % had Acanthosis nigricans.

Table 1:
Comparison of Demographic and Anthropometric Parameters in the Study Population

Parameter	PCOS (Mean±SD)	Control (Mean±SD)	t-value	p-value
Age (Years)	29.44±5.0	30.83±4.0	-1.367	0.175
Age at menarche (Years)	13.15±2.2	14.13±2.3	-1.131	0.264
Weight (Kg)	77.70±15.7	68.43±11.5	2.942	**0.004***
Height (m)	1.62±0.1	1.72±0.6	-1.124	0.264
BMI (Kg/m^2)	29.57±6.0	26.19±4.4	2.810	**0.006***
Waist circumference (m)	0.93±0.1	0.87±0.1	2.666	**0.026***
Hip-circumference (m)	1.07±0.1	1.04±0.1	1.369	0.175
Waist hip ratio (WHR)	0.87±0.1	0.83±0.1	2.304	**0.024***

*Difference is statistically significant, p<0.05. student's t-test

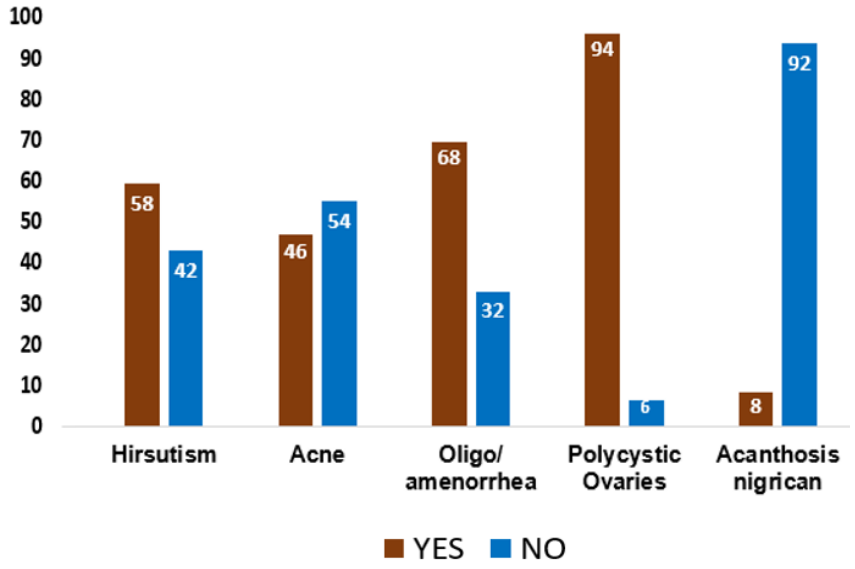

Figure 1:
Characteristics of Clinical Symptoms among PCOS Subjects.

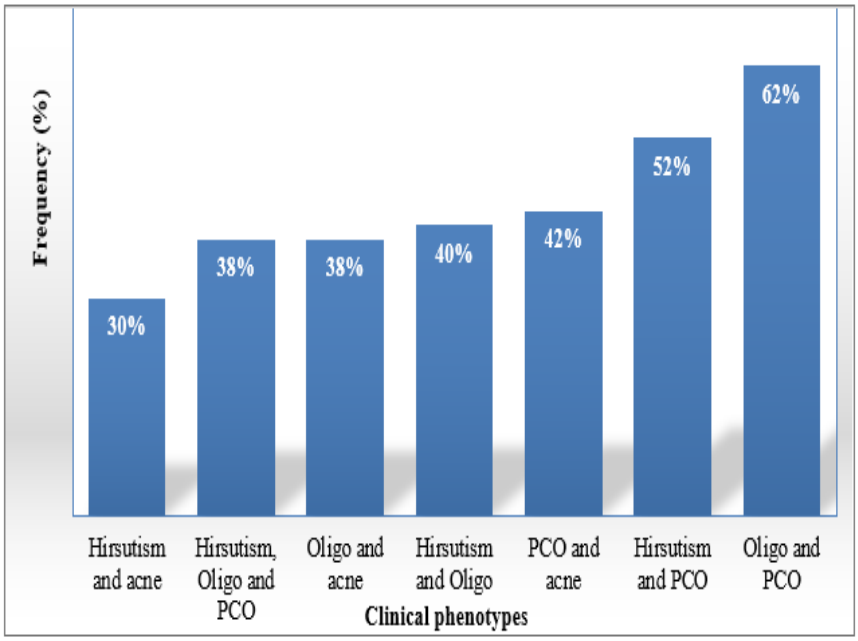

Figure 2:
Distribution of Clinical Phenotypes of PCOS in the Study Population.

Table 2:
Risk Analysis of Significant Hormonal Parameters in PCOS

Parameter	Odd ratio	95% CI	p-value
FSH	0.854	0.730-0.999	**0.049***
LH	1.037	0.986 – 1.090	0.156
LH/FSH ratio	1.691	1.162- 2.461	**0.006***
AMH	1.823	1.374 – 2.42	**0.001***
SHBG	0.987	0.977-0.998	**0.021***
Testosterone	224.8	8.418 – 6002.3	**0.001***
Estradiol	0.993	0.987-0.999	**0.021***
Prolactin	1.003	1.001-1.005	**0.016***

**Odd ratio is significantly significant, $p<0.05$*

The clinical phenotypes among the PCOS group are described in figure 2; the study shows that 62 % of cases had both PCO and Oligomenorrhea (phenotype D), 52 % had both Hirsutism and PCO (Phenotype C), 40 % had both hirsutism and Oligomenorrhea (Phenotype B), while 38 % had a combination of Hirsutism, Oligomenorrhea and PCO (Phenotype A). Table 2 shows the risk analysis of significant hormonal parameters in PCOS. (FSH, LH: FSH, AMH, testosterone, estradiol, SHBG, and prolactin) show significant odd ratio ($p<0.05$). Table 3 shows the anthropometric and hormonal comparison between the four phenotypes (A, B, C and D). The mean WHR is higher in Phenotype A (0.94 ± 0.14) compared to phenotype D (0.83 ± 0.07), $p \leq 0.05$. Figures 3a and 3b show the comparison of gonadotropins (FSH and LH) and the LH:FSH ratio. FSH (mIU/ml) was lower in PCOS [5.21(3.6-5.9)] than in control group [6.0(4.4-7.9)] ($p<0.05$). LH and LH:FSH ratio were higher in PCOS [9.23(5.4-16.6) and 2.04(1.5-3.6), respectively] than in the control group [6.36(4.0-12.6) and 1.47(0.7-2.4), respectively] ($p<0.05$). The Anti-Mullerian hormone (AMH) was higher in PCOS [4.98(3.4-7.1)] than in the control group [1.43(0.8-2.4)] ($p<0.05$) (Figure 3c).

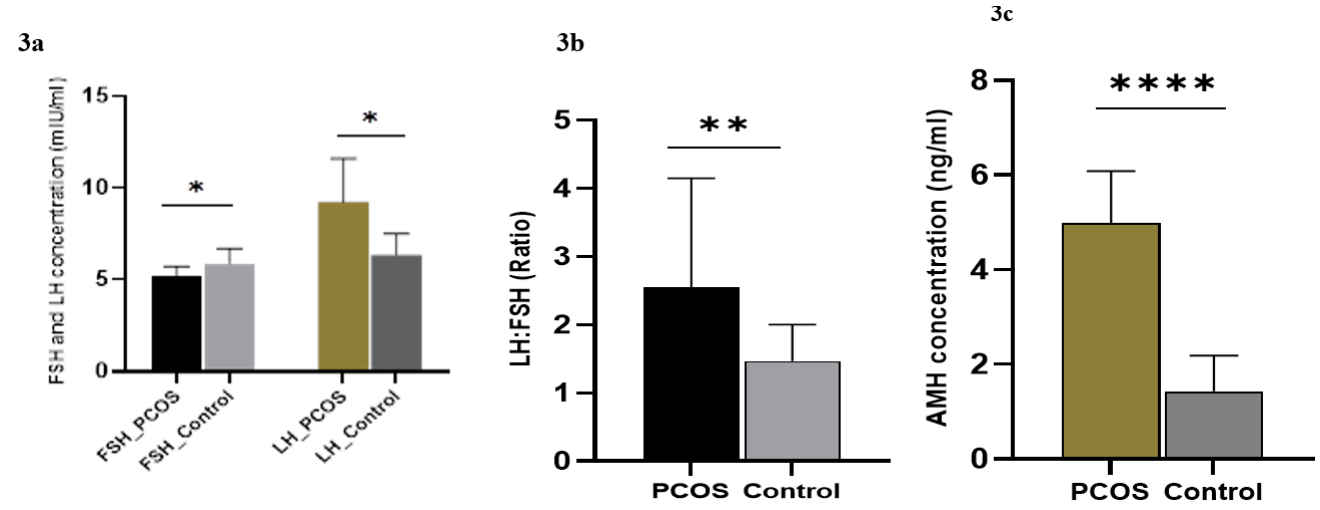

Figure 3:
Comparison of Gonadotropin and Anti-mullerian Hormones in PCOS and Controls. Values are presented as median (Q1 – Q3), using Mann-Whitney U test. Q1: 25% percentile, Q3: 75% percentile. Statistical significance is at *P<0.05, **P<0.01, ****P<0.0001

Table 3:
Anthropometric and hormonal comparison between the four phenotypes (A, B, C and D

Parameter	Phenotype A (Mean ± SD)	Phenotype B (Mean ± SD)	Phenotype C (Mean ± SD)	Phenotype D (Mean ± SD)	F-Value	P - Value
Age	30.25 ± 2.66	29.80 ± 5.61	30.57 ± 4.33	28.00 ± 5.88	0.814	0.493
Weight (kg)	85.50 ± 23.63	80.25 ± 12.10	74.24 ± 13.71	75.52 ± 14.58	1.095	0.361
Height (m)	1.66 ± 0.06	1.61 ± 0.03	1.62 ± 0.08	1.62 ± 0.07	1.235	0.308
BMI	30.89 ± 7.84	31.25 ± 5.06	28.40 ± 4.79	28.96 ± 6.57	0.616	0.608
WC (m)	0.98 ± 0.16	0.96 ± 0.13	0.94 ± 0.15	0.88 ± 0.12	1.207	0.318
HC (m)	1.05 ± 0.14	1.11 ± 0.07	1.05 ± 0.13	1.06 ± 0.08	0.691	0.562
WHR	0.94 ± 0.14	0.86 ± 0.07	0.89 ± 0.08	0.83 ± 0.07	3.216	**0.031***
FSH (mIU/ml)	5.48 ± 3.11	6.10 ± 2.42	5.12 ± 2.69	4.58 ± 1.76	1.191	0.324
LH (mIU/ml)	16.31 ± 5.97	15.36 ± 6.41	10.92 ± 2.90	10.39 ± 8.34	1.079	0.368
AMH (ng/ml)	6.64 ± 2.80	8.39 ± 4.45	5.77 ± 3.35	4.6 ± 3.44	2.542	0.068
LH:FSH (Ratio)	2.88 ± 1.48	2.72 ± 1.20	2.34 ± 1.9	2.46 ± 1.63	0.237	0.870
DHEAS (ug/dl)	123.56 ± 55.92	144.90 ± 53.76	189.33 ± 134.92	143.11 ± 60.59	0.678	0.570
SHBG (nmol/l)	37.02 ± 6.84	37.79 ± 16.83	73.96 ± 54.15	52.09 ± 36.87	2.430	0.077
Testosterone (ng/dl)	0.44 ± 0.27	0.40 ± 0.20	0.43 ± 0.11	0.28 ± 0.14	1.103	0.357
Estradiol (pg/ml)	141.17 ± 67.56	72.07 ± 32.76	114.57 ± 72.89	81.48 ± 57.62	1.911	0.141
Prolactin (uIU/ml)	459.0 ± 107.23	247.51 ± 113.99	658.97 ± 160.83	594.81 ± 110.13	1.800	0.160
Progesterone (ng/ml)	0.92 ± 0.34	0.93 ± 0.56	3.11 ± 1.37	3.85 ± 1.81	0.909	0.444

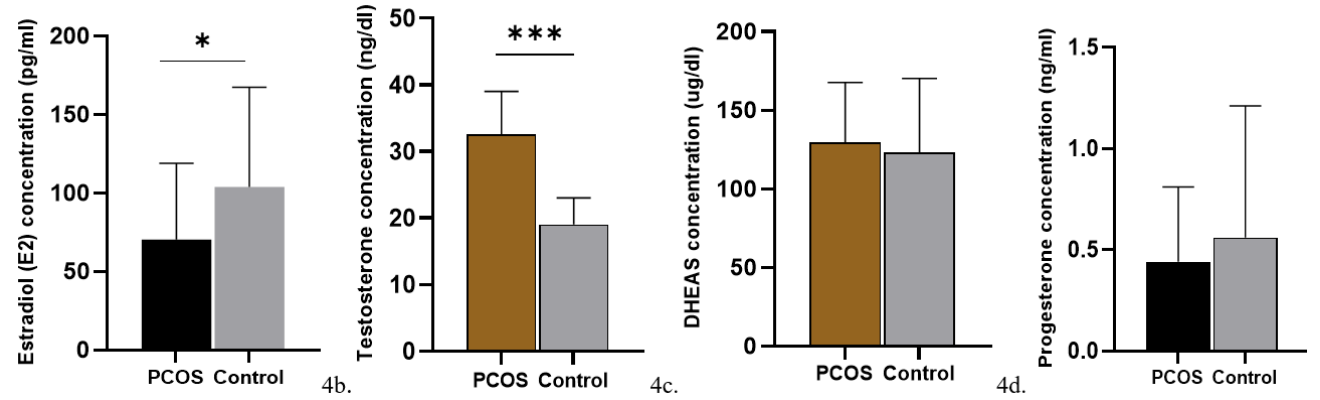

Figure 4:
Comparison of Steroid Hormones in PCOS and Controls. Values are presented as median (Q1 – Q3), using Mann-Whitney U test. Q1: 25% percentile, Q3: 75% percentile. Statistical significance is at *P<0.05, ***P<0.001

Figure 4a and 4b show the estradiol and testosterone levels respectively. Estradiol was lower in PCOS [70.45(50.5-145.9)] than in the control group [104.0(64.6-216.6)] (p<0.05), and testosterone was higher in PCOS [32.5(19.7-53.0)] than in control [19.0(12.3-29.5)] (p<0.05). There was no significant difference in the progesterone and DHEAS concentrations between PCOS and control respectively (Figure 4c and 4d). SHBG was lower in PCOS [44.85(27.3-75.7)] than in control [74.05(54.0-96.8)] (p<0.05) (Figure 5a). However, prolactin was higher in PCOS [401.6(230.9-623.0)] than in control [252.2(196.3-337.0)] (p<0.05) (Figure 5b).

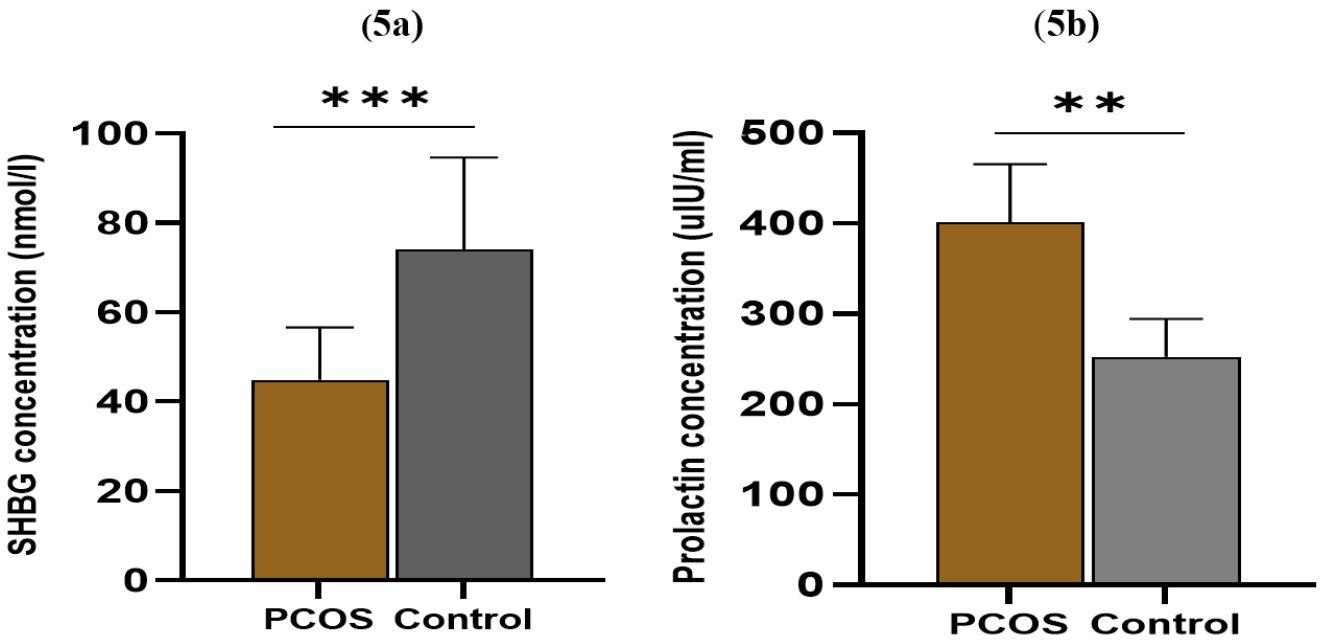

Figure 5:
Comparison of transport hormone (SHBG) and Prolactin serum levels in PCOS and control. Values are presented as median (Q1 – Q3), using Mann-Whitney U test. Q1: 25% percentile, Q3: 75% percentile. Statistical significance is at **P<0.01, ***P<0.001, ****P<0.0001

The Spearman's correlation shows a negative correlation between Estradiol and PCOS phenotypes (estimated Spearman's rho was -.310) ($p<0.05$) (Table 4). Similarly, there existed a negative correlation between AMH and PCOS phenotypes A, B, C and D (estimated Spearman's rho was -.348) ($p<0.05$) (Table 4).

Table 4:
Spearman's correlation between the Hormones and PCOS Phenotypes

Parameter	Spearman's rho	p-value
FSH	-.226	.115
LH	-.261	0.067
AMH	-.348	**.013***
SHBG	.216	.132
Testosterone	-.180	.212
Estradiol	-.310	**.028***
DHEAS	.039	.787
Progesterone	.216	.131
Prolactin	.148	.304

DISCUSSION

The understanding of the clinical phenotypes and the hormonal pattern in PCOS is necessary for proper patient classification and management. The observed phenotypes in this study were consistent with the hormonal patterns. This study demonstrated that polycystic ovary (PCO) morphology is a single popular predicting clinical feature of PCOS in Nigeria population followed by oligomenorrhea. The phenotypic occurrence of both ovulatory dysfunction and PCO morphology (Phenotype D) is the commonest phenotype of PCOS in the study population followed by hirsutism and PCO (Phenotype C). This is contrary to reports of a combination of hirsutism, oligomenorrhea and PCO (Phenotype A) described as the most prevalent in some other population (Sachdeva *et al*., 2019). The phenotypic group A is characterized by a higher prevalence of hyperandrogenism, insulin resistance, obesity, abnormal lipid profile, and metabolic syndrome, thereby presenting an increased risk of adverse metabolic and cardiovascular outcomes compared to other phenotypes especially phenotype D which has been described to represent a milder form of PCOS and considered the least severe phenotype (Sachdeva *et al*., 2019, Lizneva *et al*., 2016)

The observed elevated waist-hip ratio, which is a marker of obesity, corroborates the high prevalence of metabolic disorder in Phenotype A compared to phenotype D and other phenotypes. The elevated WHR in Phenotype A potentially indicates a higher amount of abdominal fat and, by extension, an increased risk of metabolic issues. This could explain the higher incidence of metabolic complications associated with phenotype A compared to phenotype D with lower waist-hip ratio. PCOS is a multifaceted disorder with various etiologic factors that might induce or complicate PCOS phenotypic characteristics and hormonal patterns. The occurrence of mostly phenotype D in the study population could be because of an interplay of unique hormonal, genetic and environmental factors with inherent compensatory mechanisms to prevent adverse PCOS-associated health conditions.

The observed hypogonadotropic FSH in this study suggests a follicular dysfunction in the study population and this obviously contributes to the clinical feature of oligomenorrhea/ anovulation. Similarly, the increased LH and LH: FSH are indications of the hypothalamic-pituitary ovarian axis dysfunction which favors the pulsatile release of Luteinizing hormone. The alterations in gonadotropins and ovarian steroidogenesis are major mechanisms proposed to be involved in PCOS pathophysiology (Dumesic *et al*., 2015). FSH stimulates follicular development and maturation, and its biological effects are felt on the maturation and function of the granulosa cells in the ovary. A consistent elevation of GnRH pulse frequency has been described to cause an increase in LH pulse frequency and amplitude with normal or low follicle-stimulating hormone (FSH) secretion, which results in an elevated LH:FSH ratio (McCartney *et al*., 2002, Morshed *et al*. 2021). Furthermore, observed increased AMH in the

PCOS group alludes to the presence of small (antral) follicles observed in PCOS. Naturally, AMH protein expression begins at the primary follicle stage and highest expression is detected in the pre-antral and small antral follicles, thus, elevated AMH reported in this study is an indication of presence of more antral follicles in PCOS. This suggests follicular maturation arrest in PCOS group, leading to lack of matured follicles necessary for ovulation. Thus, the elevated level of AMH together with low FSH observed in this study distinctly show follicular/ovulatory dysfunction in the PCOS study population. This agrees with similar studies which reported a higher serum level of AMH in women with PCOS compared with the control group (Parahuleva *et al*., 2013, Desforges-Bullet *et al*., 2010). While it is likely that elevated AMH contributes to the PCOS pathogenesis, the cause(s) of its elevated level remain unknown. However, LH has been reported to increase AMH production 4-fold in granulosa cells of PCOS ovaries but not of normal ovaries Pellatt *et al*. (2007).

In addition to the gonadotropins, estrogen and testosterone are two key sex steroids that have also been implicated in PCOS pathophysiology. Findings from this study showed increased testosterone and reduced estradiol concentration in PCOS. These findings indicate a physiological imbalance in steroid homeostasis, and this explains the clinical androgenicity observed in the study population. The elevated testosterone level could either be due to the increased testosterone production from the thecal cell because of LH stimulation or an accumulation of testosterone due to defects in its conversion to estradiol (because of possible decreased aromatase activity). In the normal ovary, estradiol is produced in the granulosa cell from testosterone through the catalytic action of aromatase enzyme and, FSH has been described as the primary inducer of aromatase activity and estradiol production in granulosa cell (Hobeika *et al*., 2020) The elevated level of testosterone observed in this study is mainly attributed to the ovarian theca cell origin with little or no involvement from the adrenal gland, as there was no difference in DHEAS between the PCOS and the control groups. DHEAS is gotten from the DHEA produced by the adrenal cortex and when sulfated through DHEA sulfotransferase it is released to the circulation as DHEA sulfate (DHEAS) (Goodarzi *et al*., 2015). These adrenal precursor androgens function as pre-hormones contributing largely to the amount of the more potent androgens, Testosterone, and dihydrotestosterone (DHT).

The plasma level and biological actions of sex steroids are regulated by SHBG, and sex steroids are transported by SHBG in the plasma with a high affinity for testosterone. Thus, low level of SHBG is often related to manifestations of hyperandrogenemia [22]. This baseline knowledge is consistent with the findings in this study; the serum SHBG level was lower in PCOS group compared to the control. The implication of this low serum SHBG is increase in bioavailable androgens and hyperandrogenemia which characterize PCOS pathogenesis.

Obviously, imbalance in gonadotropins and sex steroids is a major hormonal risk factor that contribute to phenotypic expression of PCOS in our study population. This is further reflected in the two predominant phenotypes (phenotype D and C) characterized by ovulatory dysfunction (oligomenorrhea), polycystic ovary morphology and hyperandrogenism (hirsutism) in our study population. The phenotypic characterisation of patients with PCOS helps in better understanding of the pathophysiology of PCOS and in predicting adverse metabolic and cardiovascular outcomes unique to our population. This will help in providing appropriate treatment options and modulating the hormones may support or improve PCOS management.

Acknowledgements

We appreciate the cooperation of the volunteers and staff of the facilities used for this study. The study was supported by the TETFund/ES/DR&D-CE/NRF2020/SETI/36/VOL.1

Ethical Statement

This study obtained informed consent from all the study participants and ethical approval was granted by the Health Research Ethics Committee, Lagos State Ministry of Health Service Commission (No. LSHSC/2222/VOL.I/64).

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