Sympathovagal Balance and Its Relationship with LH:FSH Ratio in Obese and Non-Obese Women with Polycystic Ovarian Syndrome.

Roohi Khan[1], (Dr.) Khaleel Ahmed Manik[1], (Dr.) Mohammad Hifzur Rehman[3], (Dr.) Suraiya Khanam[2], (Dr.) Gauhar Hussain[1]**

[1]Department of Physiology, Integral Institute of Medical Sciences and Research, Integral University Lucknow, U.P.
[2]Department of Obstetrics and Gynecology, Integral Institute of Medical Sciences and Research, Integral University Lucknow, U.P.
[3]Department of Physiology, Career Institute of Medical Sciences and Hospital, Lucknow, U.P.

[1]Corresponding Author :- Ms. Roohi Khan,**
Email ID: roohikhanrk6@gmail.com
Ph.D scholar in the Department of Physiology, Integral Institute of Medical Sciences and Research, Integral University, Lucknow U.P.

KEYWORDS
Obese PCOS, Non-obese PCOS, sympathovagal balance, Autonomic Function Test, Valsalva manoeuvre, Handgrip strength, Follicle-stimulating hormone and Luteinizing hormone.

ABSTRACT:
Background: Women of reproductive age are often suffered from endocrine disorder named Polycystic Ovary Syndrome (PCOS), characterised by hyperandrogenism, ovulatory dysfunction chronic in nature as well as an elevated ratio of Luteinizing Hormone (LH) to Follicle Stimulating Hormone (FSH) i.e. LH/FSH. While insulin resistance and obesity are commonly associated with PCOS, a rising number of lean and thin females are also being detected with the condition.
Aim: To evaluate sympathovagal balance through the valsalva manoeuvre and handgrip test and their relationships with the LH:FSH ratio in non-obese and obese patients with PCOS.
Material and Methods: The study involved 50 women aged 18 to 35 years, consisting of 22 patients with obese polycystic ovary syndrome (PCOS) defined by a BMI of 23 kg/m² or higher and 28 patients with non-obese PCOS, whose BMI was below 23 kg/m². Key measurements included Waist-to-Hip Ratio (WHR), levels of FSH and serum LH, handgrip strength as well as valsalva ratio for both groups.
Results: Obese patients with PCOS had significantly high WHR, BMI, & Handgrip strength compared to the other group. However, no glaring variation was seen in terms of LH:FSH ratio as well as valsalva ratio among two groups. Additionally, the valsalva ratio, Handgrip strength and the LH:FSH ratio were not significantly correlated with each other.
Conclusion: The study concluded that PCOS women exhibit altered sympathovagal balance, with reduced parasympathetic activity and elevated sympathetic tone. Obese PCOS patients showed greater handgrip strength compared to their non-obese counterparts. Higher BMI in females with PCOS was linked with higher WHR. However, major variances were not observed among two groups in terms of endocrinological parameters. Further, the Valsalva ratio, Handgrip strength and the FSH/LH ratio were not significantly correlated with each other.

INTRODUCTION

The most common endocrine disorder in the reproductive age group is Polycystic ovary syndrome (PCOS), 7% to 10% of females are affected by it worldwide [1,2]. Common symptoms in women with PCOS include insulin resistance, menstrual irregularities, metabolic syndrome, hypertension, and hyperandrogenism[1]. Heterogeneous disorders due to excess androgen manifests with varying levels of dysfunctions are metabolic as well as reproductive in nature. PCOS is also linked to metabolic syndrome insulin resistance (IR).[3] A significant threat is presented by these comorbidities to an individual's health and substantially affects the populations by lowering quality of life. Advancement of medicine have enhanced the understanding of PCOS.[4]

PCOS diagnosis is carried out on criteria of Rotterdam, this mandatorily needs occurrence of at least two out of three indicators: polycystic ovaries, anovulatory cycles, or hyperandrogenism[5]. Polycystic ovarian morphology is confirmed through transvaginal ultrasonography, which should show either

follicles in each ovary of 2-9 mm in diameter and quantity 12 or more or enhanced ovarian volume of more than 10 mL without a dominant follicle >10 mm.[6] Theoretically, PCOS arises from a complex interplay of behavioural, environmental, and genetic factors[7,8]. Abnormalities in the adrenal axis or hypothalamic-pituitary-ovarian adds significantly to the condition of pathophysiology. A disruption in the pattern of secretion gonadotropin-releasing hormone (GnRH) leads to a comparative spike of LH compared to release of FSH. Ovarian oestrogen is implicated in creating an abnormal feedback mechanism that elevates LH levels. Typical ranges of ratio of LH to FSH is 1 to 2 among healthy females. However, among women with PCOS, this ratio is seen to reach in the range of 2 or 3. Consequently, the elevated LH:FSH ratio inhibits ovulation in PCOS patients.[9] The primary treatment for PCOS focuses on lifestyle modifications, particularly weight loss. While PCOS is commonly linked to obesity and insulin resistance, an increasing number of lean women are also being diagnosed with the condition[10]. Both lean and overweight women can display these metabolic characteristics, which are significant etiological factors in PCOS.[11]

Some literature has annotated varying levels of parasympathetic as well as sympathetic function & response of the body among the population affected by PCOS, contributing to cardiac pathology in affected patients. The leading causes of mortality among females are cardiovascular disease, and certain studies have indicated the presence of risk factors contributing to cardiovascular disease in females having PCOS during early adulthood. India, approximately has 46.9 million individuals are believed to suffer from cardiovascular disease.[12] Several studies found patients having PCOS showing autonomic dysfunction, characterised by a enhanced response for sympathetic nervous system while poor response to parasympathetic nervous system compared to counterparts which were normal.[13]

The body's overall function is primarily regulated by nervous systems which may be either parasympathetic and sympathetic. Neurotransmitters, specifically norepinephrine (NE) and acetylcholine (ACh), are crucial for nerve function. Ach is released by pre as well as postganglionic neurons in the parasympathetic system. In autonomic ganglia the nicotinic receptors are acted upon by presynaptic Ach, while muscarinic receptors of organs which are targeted are affected by postsynaptic ACh. Postganglionic neurons discharge NE and preganglionic discharges ACh in the sympathetic system, this act as key neurotransmitter. The targeted organs have adrenergic receptors namely alpha (α) & beta (β) which are acted upon by NE.[14] Recent studies have increasingly shown that autonomic dysfunction contributes to the progression of PCOS.[15,16] The function of the ovary is regulated not just by hormones, but also by neural signals. Neural innervation involves sympathetic ovarian plexus as well as superior ovarian nerve, which originate in segment of upper lumbar via visceral nerve fibres, as well as parasympathetic input through the vagus nerve, controlled by central nervous system (CNS).[17] Previous research in humans has shown that sympathetic nerve activity influences ovarian steroid production, follicle growth, and the ovulation process.[18]

Many women with PCOS experience increased sympathetic nervous system activity, often without realising it. This heightened sympathetic tone related to anovulation, menstrual irregularities and elevated levels of androgen, which can contribute to the development of PCOS.[19,20,21] Symptoms of elevated sympathetic activity include a reduced variability of heart rate, increased rate of heart in resting state, heightened blood pressure: systolic in physical activity, hypertension, post-exercise slower recovery of heart rate, elevated muscle sympathetic nerve activity, enhanced levels in adrenergic metabolites in urine as well as serum. [18,21] Persistent sympathetic overactivity is also linked to central obesity, with the presence of obesity further exacerbating this overactivity.[22,23]

Obesity and PCOS often exacerbate each other in a continuous cycle, with each condition worsening the other. Research indicates that between 30% and 75% of women with PCOS are also affected by obesity.[5] However, many researchers have found that women, regardless of whether they are lean or overweight, often exhibit these metabolic characteristics, which are considered significant etiological factors in PCOS.[11] Research suggests that women with PCOS frequently show impaired

sympathovagal balance characterised by reduced parasympathetic (vagal) activity[19] and increased sympathetic nervous system activity.[20]

The Valsalva manoeuvre test is non-invasive in nature employed to evaluate autonomic neuropathy related to cardiac functions[24]. It evaluates sympathetic adrenergic functions through responses related to blood pressure while responses related to heart rate are used for cardiovagal (parasympathetic) functions.[25.] The Valsalva ratio, defined as the ratio of the longest RR interval after the expiratory strain to the shortest RR interval during the strain, serves as an indicator of parasympathetic function. Additionally, baroreflex sensitivity (BRS) can be assessed through Valsalva manoeuvre by evaluating regression line slope of the between and systolic blood pressure and RR intervals values during manoeuvre phases II as well as IV.[26,27]. The Valsalva manoeuvre involves increasing intrathoracic pressure, which reduces the heart's preload. The decreased preload results in compensatory reflex mechanisms as well as baroreflex engagement and in turn leads to cardiovascular changes during and post manoeuvre. This highlights contraindications as well as indications and for execution of Valsalva manoeuvre, it also emphasises importance of the interprofessional group who uses particular test in autonomic dysfunction assessment.[27] Handgrip strength, assessed noninvasively, shows pinnacle force in static state generated by hand by squeezing a dynamometer.[28] Handgrip strength (HGS) denotes amount of force required to grip anything and is essential for performing various everyday tasks. It serves as a valuable indicator in numerous clinical contexts and can be measured easily and affordably. Additionally, HGS is linked to several chronic diseases.[29]

Although there is existing research on parasympathetic as well as sympathetic reactivity among females who are obese and having PCOS, studies focusing on lean women are limited. Therefore, our aim is to explore autonomic function, its affiliation with FSH, LH hormonal levels in PCOS patients including both non obese and obese. We hypothesise that there exists insignificant variance among the two groups in hormonal parameters or autonomic function.

MATERIAL AND METHODS

Ethical Clearance: This study has been performed with proper ethical sanction of Institutional Ethics Committee of the college (IEC/IIMS&R/2022/07)

Study Design: A cross-sectional observational study involving 50 females having PCOS who visited the Integral Institute of Medical Sciences and Research, Lucknow.

Inclusion criteria:

1. All participants must provide written informed consent.
2. The study included the patients of reproductive age (18-35 years) who have been newly diagnosed with PCOS (within the past 6 months).

Exclusion criteria:

1. Patients with endocrine disorders such as hypothalamic or pituitary dysfunction, diabetes, etc.[5]
2. Patients with any of cardiovascular disorders.
3. Patients diagnosed with PCOS for more than 6 months and currently undergoing treatment were excluded.

Rotterdam Criteria for PCOS

The Rotterdam criteria were utilised to select PCOS patients, with the diagnosis uses basis of occurrence of minimum two out of three symptoms mentioned below:[30]

1. Anovulation or oligo-ovulation.
2. Clinical hyperandrogenism
3. The presence of polycystic ovaries.

Hormonal Assays

This study was conducted with newly diagnosed PCOS women (diagnosed within the last 6 months) of reproductive age (18-35 years) who attended the Gynecology OPD at Integral Institute of Medical

Sciences and Research, Lucknow. A comprehensive medical history, including menstrual history, was recorded for each participant. Samples of blood for luteinizing hormone (LH) assays as well as follicle-stimulating hormone (FSH) taken on the 2nd or 3rd day of menstrual cycle in which the follicular phase was progesterone-induced or spontaneous. Normal values for FSH were considered to be between 3.9 and 12 mIU/ml. Normal values of LH defined as 1.5 to 8 mIU/ml, with an LH:FSH ratio of 2:1 considered significant. Hormonal parameters, including serum levels of TSH, FSH, LH, prolactin, testosterone, all measured using VIDAS Hormone Analyser. These measurements were then compared between two groups of PCOS females including both the non-obese and obese .[31-33]

Anthropometric Data

Additionally, anthropometric data were collected from the patients as follows:

- **Height** (in metres) was taken with a stadiometer after removing shoes.
- **Weight** (in kilograms) was taken with clothing very light in nature using a weighing machine (Ramson Surgical Company).
- **Waist-Hip Ratio** was annotated by measuring circumference of waist at the slimmest part between the iliac crest and lowest rib, and the circumference of the hips at the widest area of the buttocks using a measuring tape.
- **Body Mass Index (BMI)** was calculated by weight in kilograms (kg)/ height in metres squared (m^2)

The PCOS women classified in groups based on BMI criteria for Asians:

- A BMI of normal range (18-22.9 kg/m²) was designated as the non-obese PCOS group.
- A BMI of overweight and obese category (≥23 kg/m²) was designated as the obese PCOS group.

Autonomic function tests

Previous researchers have employed various methods to measure autonomic functions; however, we concentrated on a select few tests. These tests were conducted on both non obese as well as obese females with PCOS in the Physiology Department of Integral Institute of Medical Sciences and Research, Lucknow.

1. **For the evaluation of parasympathetic nervous system functions: (Valsalva manoeuvre)[33 & 34]**
   The participants were instructed to blow into a sphygmomanometer connected with a mouthpiece, maintaining at 40 mmHg expiratory pressure for 15 seconds, then releasing the pressure at 15th second. An ECG was recorded from lead II for about 1 minute for obtaining reference values and uninterrupted regular monitoring throughout the manoeuvre and for 45 seconds following the release of respiratory strain. Valsalva ratios were determined by dividing the R-R interval (longest) post manoeuvre by the R-R interval (shortest) during or shortly post manoeuvre, using Medicaid physio-pac 8 channel digital polygraph. A ratio of >1.20 was considered normal, while ≤ 1.20 ratio was treated abnormal

   1VR = Longest R-R interval after manoeuvre (Phase IV) /Shortest R-R interval during test (Phase II).

2. **Evaluation of sympathetic nervous system functions: (Handgrip Dynamometer test)[34]**
   Diastolic Blood Pressure (DBP) changes were measured during the isometric handgrip test (HGT). Baseline BP was recorded using a My Cure (Model no. XY-B02) digital blood pressure monitor. Subjects then performed maximum voluntary contraction (MVC) by gripping a handgrip dynamometer with their dominant hand as hard as possible for a few seconds, and the maximum force exerted was recorded. Subsequently, they were instructed to press the dynamometer at 30% of their MVC every minute using their dominant hand. The difference between the resting DBP reading and the reading just before releasing the handgrip was recorded as ΔDBP in the HGT.

These results were compared between obese and non-obese PCOS groups.

STATISTICAL ANALYSIS

SPSS version 29 was used for Statistical analysis published by IBM, USA. Data represented as Mean ± SD (Standard Deviation). To determine differences among two groups unpaired two-tailed Student's t-tests were utilised. A p-value of ≤ 0.01 treated extremely significant while for statistical purposes a p-value of ≤ 0.05 was taken significant. For assessment of association among two quantifiable variables Pearson correlation was considered, also for checking significance of the correlation 't-test' was used. Correlation coefficient (r) indicated presence of direct correlation (positive) or inverse correlation (negative) relationship.

RESULTS

This cross-sectional study included 28 non-obese PCOS women (BMI <23 kg/m²) as well as 22 obese women with PCOS (BMI ≥23 kg/m²), PCOS diagnosis was done using Rotterdam ESHRE/ASRM sponsored PCOS consensus criteria

Comparison of the anthropometric data between the study groups.

There was no statistically significant age difference among two groups (23.41 ± 3.065 years for the obese PCOS group versus 21.93 ± 2.62 years for the non-obese PCOS group). Though, among obese PCOS group the WHR and BMI were significantly higher in comparison with other group, with BMI values of 28.67 ± 6.47 kg/m² versus 20.445 ± 1.74 kg/m²
(p = <0.01) and WHR values of 0.862 ± 0.062 versus 0.80 ± 0.04 (p = <0.01), respectively. The comparison of anthropometric analysis results between the two groups is presented in Table 1.

Comparison of hormone levels between the study groups.

Serum LH:FSH ratio, LH and FSH levels of two groups were recorded comparable. Though, high BMI group patients did not show statistically substantial variances for serum levels of FSH and LH in comparison with normal BMI group (FSH: 6.176±2.190 mIU/ml vs. 6.100±1.737 mIU/ml; p=0.892) and (LH: 10.727±5.97 mIU/ml vs. 10.795±4.381 mIU/ml; p=0.963), respectively. The LH:FSH ratio recorded 1.781±1.044 among high BMI groups while 1.709±0.483 with normal BMI groups (p=0.748). Two groups were compared for results of biochemical analysis which is depicted in Table 1.

Comparison of autonomic function tests between the study groups.

The ΔDBP_{ihg} values of obese PCOS patients were substantially higher in comparison to PCOS patients who were non-obese (28.23±1.80 mmHg vs. 24.07±1.54 mmHg, p=<0.01). However, the Valsalva ratio didn't reveal statistically substantial variance among obese (1.2±0.15) and non-obese PCOS patients (1.25±0.073, p=0.128). The comparison of autonomic function test results between the two groups is presented in Table 1.

Correlation between autonomic function tests and hormonal assays.

Negative correlation presented by Valsalva ratio for LH:FSH ratio (r = - 0.151), which was not significant statistically (p = 0.294). Additionally, positive correlation (r = 0.052) observed among ΔDBPihg and LH-FSH ratio in PCOS patients, however that too was insignificant statistically (p = 0.722). The correlations between autonomic function tests and hormonal levels are detailed in Table 2.

TABLE NO.1 Comparison of Autonomic status and Hormonal Parameters amongst obese and non obese PCOS women

Parameters	**Obese PCOS Women (n=22)** **mean+SD**	**Non- Obese PCOS Women (n=28)** **mean+SD**	**p-value**
Age	23.41±3.065	21.93±2.62	0.072
BMI	28.67±6.47	20.445±1.74	<0.01**
WHR	0.862±0.062	0.80± 0.04	<0.01**
FSH (mIU/ml)	6.176±2.190	6.100±1.737	0.892
LH (mIU/ml)	10.727±5.97	10.795±4.381	0.963
LH:FSH ratio	1.781±1.044	1.709±0.483	0.748
ΔDBP_{ihg}	28.23±1.80	24.07± 1.54	<0.01**
Valsalva Ratio	1.2±0.15	1.25±0.073	0.128

Data are presented as mean±SD. Unpaired two-tailed t-test was used. p ≤0.05* considered as statistically significant, p≤0.01** considered as highly statistically significant.
BMI: Body Mass Index. WHR: Waist-Hip Ratio. FSH: Follicle Stimulating Hormone. LH: Luteinizing Hormone
$\Delta DBP_{ihg:}$ Difference of baseline Diastolic Blood Pressure and maximum diastolic blood pressure in isometric handgrip test.

TABLE NO.2. Pearson's Correlation among the variables in PCOS women

	Valsalva Ratio		**ΔDBPihg**	
Hormonal Levels	**Coefficient (r)**	**p-value**	**Coefficient (r)**	**p-value**
FSH (mIU/ml)	-0.145	0.314	0.087	0.547
LH (mIU/ml)	-0.172	0.233	0.024	0.853
LH:FSH ratio	-0.151	0.294	0.052	0.722

p ≤ 0.05* considered as statistically significant *, (r) considered as correlation coefficient.
FSH: Follicle Stimulating Hormone
LH: Luteinizing Hormone
ΔDBP_{ihg} : difference of baseline diastolic blood pressure and maximum diastolic blood pressure in isometric handgrip test.

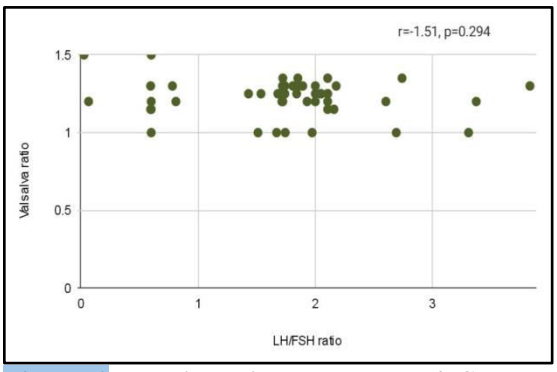

Figure.1 Relationship between LH/FSH and Valsalva ratio

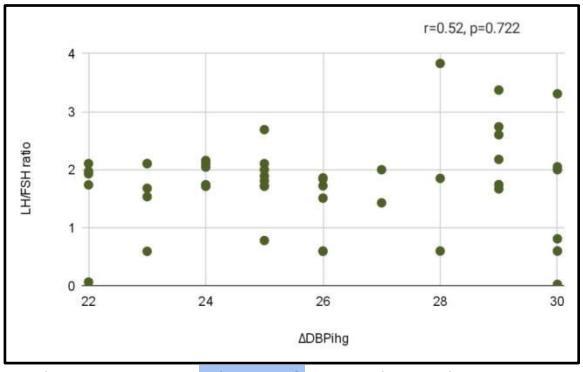

Figure.2 Relationship between Valsalva ratio and ΔDBPihg

DISCUSSION

Results indicate two groups having high as well as normal BMI and had similar Waist-to-Hip Ratio (WHR), LH:FSH ratio, Valsalva ratio, and ΔDBPihg. Furthermore, the population under study shows almost insignificant correlation among the LH:FSH ratio and autonomic function tests.

A high or above-average BMI was noticed among the majority (80%) of females having PCOS and also show symptoms such as hirsutism, acne, male-pattern baldness and ovarian cysts. Several females among them do not go undetected until in their adulthood they confront issues related to fertility. Conversely, few females having PCOS but BMI being in low or normal category might not face insulin resistance and may show typical symptoms of pubertal maturation in adolescence, like menstrual cycles irregularity, potential depression as well as acne. However, obese PCOS females may have different PCOS pathophysiology.

In PCOS, there exists disruption of the normal gonadotropin axis, resulting in reduced levels of FSH while increased levels of LH, which reverses the LH:FSH ratio. Our study observed in both obese as well as lean females with PCOS have elevated ratio of LH/FSH ratio and increased serum LH levels, similar findings reported by **Saxena P et al.**[35,36] Our study's results similar with the findings of **Bindal J et al**[37], but contrast with those of **Ramanand et al**[37]**.** When comparing females with PCOS having obese /overweight with normal weight it was noticed that ratio of LH:FSH and LH found increased w.r.t. those within normal weight, with a highly significant difference in LH:FSH ratio. **Lal et al.**[38] observed differences with significant levels in LH:FSH ratio, FSH and LH, among non-obese as well as obese females. Based on these findings, they recommended that obese participants focus on weight loss and lifestyle changes.

In this study, PCOS patients displayed obesity at the central abdominal region. Mechanisms causing obesity of the central abdominal region that leads to increased sympathetic activity are not fully understood. However, it is observed that fat cells in these individuals have heightened sensitivity to lipolytic agents, and factors that stimulate fat mobilisation are activated.[33] Further it is reinforced by findings that isolated adipocytes from visceral fat depot of PCOS female exhibited amplified catecholamine-stimulated lipolysis.[33] It's important to note that sympathetic nerve activity is more strongly linked to visceral fat as compared to subcutaneous or total fat mass.[39,40] Sympathetic nerve activity is elevated in obesity of central abdominal region also if hypertension is not present.[33] During isometric exercise, metabolites such as lactic acid and adenosine typically increase in concentration. These metabolites are found by nerve endings which are metabolite-sensitive among the skeletal muscle

interstitium. This detection stimulates group IV (metaboreceptor) afferent fibres, starting a strong reflex enhancing activity of the sympathetic nerve. Consequently, it results in vasoconstriction, leading to an increase of blood pressure.[40] However, in normal individuals, it returns to baseline within 2 minutes after stopping the exercise. **Saranya et al**[19] and **Sharma V et al**[31] observed an increase in diastolic blood pressure (DBP) in PCOS patients during isometric handgrip exercise, this remains consistent with present study and its findings. Additionally, our study found that women with obese PCOS had greater handgrip strength compared to women with non-obese PCOS. **Hashim ZH et al**[33] and **Shrivastava R et al**[41] saw differences which were insignificant statistically in the Valsalva ratio between non-obese as well as obese females having PCOS; this also remains consistent with our current study's outcome. In contrast, **Sukhera et al**[42], **Akhter A et al**[43] and **Sharma V et al**[31] found reduced vagal activity in PCOS patients compared to controls when examining parasympathetic reactivity through Valsalva ratios.

CONCLUSION

The study concludes females having PCOS, at rest display varied cardiac autonomic modulation, characterised by elevated sympathetic and diminished parasympathetic tone. Additionally, obese PCOS women have greater handgrip strength in comparison with their counterparts who are non-obese. This highlights the importance of non-invasive screening techniques, such as autonomic function tests (AFTs), for PCOS patients. No significant correlation was found between the Valsalva ratio, handgrip strength, and the LH:FSH ratio. Moreover, in females with PCOS elevated BMI shows association with higher Waist-Hip Ratio (WHR), but there is no difference in the LH:FSH ratio between obese and non-obese groups. Future research involving a large multicentric study on Asian populations is needed to explore the endocrine alterations spectrum in PCOS across varied BMI categories. Weight management as well as annual monitoring of lipid profiles are recommended to avoid metabolic problems among females who are obese with PCOS.

LIMITATIONS

The BMI threshold applied in our study was derived from the consensus guidelines for the Asian population. Additionally, our study had a small sample size.

Declarations:
Conflicts of interest: There is not any conflict of interest associated with this study
Consent to participate: There is consent to participate.
Consent for publication: There is consent for the publication of this paper.
Authors' contributions: Author equally contributed the work.

Acknowledgements
The Author and Co- Authors extend their sincere gratitude to Integral University, Lucknow for their immense support and provision of the important facilities to carry out this research smoothly. This study was conducted under assigned manuscript number MCN IU/R&D/2024-MCN0003273, in accordance with the University guidelines.

REFERENCES

1. Ghatnatti V, Patil S, Kour H. Assessment of clinical, biochemical, and hormonal profile of lean versus overweight polycystic ovarian syndrome patients: a cross-sectional study. APIK J Intern Med. 2022;10(1):13-6.
2. El Hayek S, Bitar L, Hamdar LH, Mirza FG, Daoud G. Poly cystic ovarian syndrome: an updated overview. Front Physiol. 2016;7:124.

3. Kamrul-Hasan AB, Aalpona FT. Comparison of clinical, metabolic, and hormonal parameters in lean vs. obese women with polycystic ovary syndrome: a single-centre study from Bangladesh. Sri Lanka J Diabetes Endocrinol Metab. 2021;11:15-25.
4. Stone T, Leone C, Ayers T, Stachenfeld N. Autonomic Dysfunction in Women with Androgen Excess PCOS. The FASEB Journal. 2020; 34(S1):1-1
5. Sachdeva G, Gainder S, Suri V, Sachdeva N, Chopra S. Obese and Non-obese Polycystic Ovarian Syndrome: Comparison of Clinical, Metabolic, Hormonal Parameters, and their Differential Response to Clomiphene. Indian J Endocrinol Metab. 2019;23(2):1-6.
6. Setji TL, Brown AJ. Polycystic Ovary Syndrome: Update on Diagnosis And Treatment. The American Journal of Medicine.October 2014;127(10):912-919.
7. Ollila MM , Kiviniemi AM, Victorin ES, Puukka K, Ruokonen A, Tapanainen JS et al. Women with PCOS display reduced cardiac vagal activity which is dependent on metabolic abnormalities. InEndocrine Abstracts. 2018;56.
8. Conway G, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Franks S, Gambineri A, et al. The polycystic ovary syndrome: a position statement from the European Society of Endocrinology. Eur J Endocrinol. 2014 Oct; 171(4): P1-29.
9. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and treatment of polycystic ovary syndrome: an endocrine society clinical practice guideline.Reprod Endocrinol. 2014; 0(20): 22-35
10. Saadia Z. Follicle Stimulating Hormone (LH: FSH) Ratio in Polycystic Ovary Syndrome (PCOS) - Obese vs. Non-Obese Women. MED ARCH. 2020; 74(4): 289-293.
11. Fatima N, Perween S , Ansari S, Miyan F, Ahsan F , Ajmal M et al. Study of Drugs prescribed and adverse drug reaction in polycystic ovarian syndrome and menstrual disorder in Gynaecology Department at Integral Institute of Medical Sciences and Research, Lucknow, India.Int. J. Adv. Res.; 11(08): 848-858.
12. Bano R, Swami D, Ahmad N. Study of Association of Anthropometric Parameters of Obesity and Blood Pressure in Hypertensive Subjects in A Tertiary Care Hospital. Indian Journal of Applied Research. October 2016; 6(10): 55-56.
13. Goyal M, Dawood AS. Debates Regarding Lean Patients with Polycystic Ovary Syndrome: A Narrative Review. J Hum Reprod Sci. 2017; 10(3): 154-161.
14. Wehrwein EA, Orer HS, Barman SM. Overview of the Anatomy, Physiology, and pharmacology of the autonomic nervous system. Compr Physiol. 2016;6(3):1239-1278.
15. Velusami D, Sivasubramanian S. Sympathovagal imbalance and neurophysiologic cognitive assessment using evoked potentials in polycystic ovary syndrome in young adolescents—a cross-sectional study. J Basic Clin Physiol Pharmacol. 2018;30(2):233-237.
16. Li W, Chen Y, Xu L. Association of sympathetic nervous system activity with polycystic ovarian syndrome. Clin Exp Obstet Gynecol. 2014;41(5):499-506.
17. Brauer MM, Smith PG. Estrogen and female reproductive tract innervation: Cellular and molecular mechanisms of autonomic neuroplasticity. Auton Neurosci. 2015;187:1–17.
18. Luna SL, Neuman S, Aguilera J, Brown DI, Lara HE. In vivo beta-adrenergic blockade by propranolol prevents isoproterenol-induced polycystic ovary in adult rats. Horm Metab Res. 2012;44:676.
19. Saranya K, Pal GK, Habeebullah S. Assessment of cardiovascular autonomic function in patients with polycystic ovary syndrome. J Obstet Gynaecol Res 2014;40:192–9.
20. Lambert EA, Teede H, Sari CI. Sympathetic activation and endothelial dysfunction in polycystic ovary syndrome are not explained by either obesity or insulin resistance. Clin Endocrinol 2015;83:812–9.
21. Dag ZO, Alpha M, Turkel Y, Isik Y. Autonomic dysfunction in patients with polycystic ovary syndrome. Taiwan J Obstet Gynecol. 2015;54(4):381-384.
22. Canale MP, Manca di Villahermosa S, Martino G. Obesity-related metabolic syndrome: mechanisms of sympathetic overactivity. Int J Endocrinol. 2013;2013:865965.

23. Thorp AA, Schlaich MP. Relevance of sympathetic nervous system activation in obesity and metabolic syndrome. J Diabetes Res. 2015;2015:341583.
24. Nagar A, Dhingra N. Valsalva retinopathy. Postgrad Med J. 2017 Mar;93(1097):174.
25. Novak P. Quantitative Autonomic Testing.J Vis Exp. 2011;(53):2502
26. El-Khayat AR. Valsalva hemorrhagic retinopathy in pregnancy after yoga. BMJ Case Rep. 2017 Aug 11;2017
27. Won HJ, Kim PN, Lee JS. Changes in echogenicity of hepatic hemangiomas during the valsalva manoeuvre. J Clin Ultrasound. 2017 Jul 08;45(6):328-331
28. Kim CR, Jeon YJ, Kim MC, Jeong T, Koo WR. Reference values for hand grip strength in the South Korean population. PLoS One. 2018;13(4)
29. Lee SH, Gong HS. Measurement and Interpretation of Handgrip Strength for Research on Sarcopenia and Osteoporosis. J Bone Metab. 2020 May;27(2):85-96
30. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group . Revised 2003. consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004; 19(1): 41–47.
31. Sharma V, Shukla J, Mittal P, Amita. The Comparison of Cardiac Autonomic Functions in Patients With Polycystic Ovarian Syndrome and Healthy Controls.International Journal of Pharmaceutical and Clinical Research 2023; 15(4); 435-440.
32. Kanazawa M, Yoshiike N, Osaka T, Numba Y, Zimmet P and Inoue S. Criteria and classification of obesity in Japan and Asia-Oceania. Asia Pacific J Clin Nutr 2002; 11: S732–S737
33. Hashim ZH, Hamdan FB, Rashid Al-Salihi A. Autonomic dysfunction in women with polycystic ovary syndrome. Iran J Reprod Med. 2015; 13(1): 27–34.
34. Pattnaik S, Gupta S, Saxena U, Matlani M, Kapoor R. Comparison of autonomic function tests and high-sensitivity C-reactivity protein in overweight patients of polycystic ovarian syndrome and overweight controls. Indian J Physiol Pharmacol 2020;64(4):303-8.
35. Saxena P, Prakash A, Nigam A, Mishra A. PCOS: is obesity a sine qua non? a clinical, hormonal, and metabolic assessment in relation to BMI. Indian J Endocrinol Metab. 2012;16(6):996-9
36. Bhindal J, Jain R. Clinical and Hormonal Profile in Non Obese Women of Polycystic Ovarian Syndrome. Journal of Medical Science and Clinical Research. 2018;6(8):467-473
37. Ramanand SJ, Ghongane BB, Ramanand BJ, Patwardhan HM, Patwardhan VM. Hormonal profile of polycystic ovary syndrome (PCOS) in Indian women. RJPBCS. 2012 Dec; 3 (4): 1159.
38. Lal L, Bharti A, Perween A. To Study The Status of LH: FSH Ratio in Obese And Non-Obese Patients of Polycystic Ovarian Syndrome. IOSR J Dent Med Sci. 2017; 16(01): 20-23
39. Lansdowne A, Rees AD. The Sympathetic Nervous System in Polycystic Ovary Syndrome: a novel therapeutic target? Clin Endocrinol (Oxf) 2012; 77: 791-801
40. Garg R, Malhotra V, Dhar U, Tripathi Y. The isometric handgrip exercise as a test for unmasking hypertension in the offsprings of hypertensive parents. J Clin Diagn Res. 2013;7(6):996-9.
41. Shrivastava R, Pathak T, Shrivastava P, Patel S, Chouhan S, Singh R, Parashar R, Mishra S. Assessment of cardiac autonomic function in women with polycystic ovary syndrome through Ewing's battery, heart rate variability analysis, and Composite Autonomic Symptom Score-31 scale. Cureus. 2023 Sep 19;15(9):e45580.
42. Sukhera S, Ilyas J, Iqbal S, Mastoor M, Zaman Q. Parasympathetic Reactivity and Oxidative Stress among Participants Suffering from Polycystic Ovarian Syndrome. Pakistan Journal of Medical & Health Sciences. 2022 Jul 23;16(05):1126.
43. Akhter A, Ferdousi S, Sultana S, Mostafa M. Relationship between parasympathetic reactivity and oxidative stress in polycystic ovary syndrome. Journal of Bangladesh Society of Physiologist. 2020;14(2):48–55.