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DearColleagues,

As of January 2023, our "**Journal of Controversies Obstetrics&Gynecology and Pediatrics**" has been published under the Medihealth Academy to publish all articles, reviews and case reports on Pediatrics, especially in the field of Obstetrics and Gynecology. This year JCOGP has been achieved in a rapid way with an increasing acceleration.

In the three volumes of 2023, we published at most two letter to the editor, at least 10 research articles, and 5 review paper. In each volume of JCOGP, we try to publish articles that contain current topics and create excitement in the field Obstetrics and Gynecology and Pediatrics for readers. The articles that will be published are planned according to acceptance order. Referee and download status of the manuscripts are posted on our journal's web site. To guide the authors, the statistics tab of our journal website, acceptance, rejection, and assessment durations of the candidate articles are shared with the authors.

Without the ethical permission no articles could be shared in our journal. In the forth volume, I would like to thank all academics who accepted to be referees and assessed the articles.

We are pleasure to see the increase in the number of articles which needs for multiple assessment by a referee and hence, endless thanks to all our referees including the Editors and the Editorial board.

Lastly, I would like to congratulate all the authors whose articles have been published in the year 2023 and hope to see you all in the new volumes in 2024.

Cordially Yours…

Prof. Oya GÖKMEN, MD
Honorary Editor in Chief

Journal of
Controversies in Obstetrics & Gynecology and Pediatrics

Volume: 1 Issue: 4 Year: 2023

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Original Article

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The relationship between prolactin level and inflammatory markers in women with polycystic ovary syndrome

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ABSTRACT

Aims: This study aimed to investigate the relationship between prolactin (PRL) levels and inflammatory markers in women with polycystic ovary syndrome (PCOS) compared to controls.

Methods: A total of 120 women, 60 with PCOS and 60 controls, were included in this study. The participants were divided into four groups based on their PRL levels: Hyperprolactinemia (HPRL) PCOS, normal PRL PCOS, HPRL controls, and normal PRL controls. The levels of various inflammatory markers, including C-reactive protein (CRP), Hemoglobin (Hb), red cell distribution width (RDW-SD), mean platelet volume (MPV), and platelet distribution width (PDW), were measured and compared between the groups. The correlation between PRL levels and inflammatory markers was also analyzed.

Results: The results show that the mean value of CRP was higher in the PCOS group with HPRL (2.15±1.61) compared to the PCOS group with normal PRL levels (1.68±1.19), but the difference was not statistically significant (p=0.432).The correlation results show that there was a statistically significant negative correlation between PRL levels and Hb (r=-0.313, p=0.015) and a positive correlation between PRL levels and RDW-SD (r=0.352, p=0.006) in PCOS patients.In PCOS patients, higher PRL levels were associated with increased RDW-SD, decreased Hb levels, decreased platelet count, and increased MPV and PDW. However, there was no significant correlation between PRL levels and inflammatory markers in the control group.

Conclusion: The results of this study suggest that higher PRL levels may be associated with increased inflammation in PCOS patients. However, further research is needed to understand the underlying mechanisms and potential clinical implications of these associations.

Keywords: Polycystic ovary syndrome, prolactin, inflammatory markers, inflammatory markers, PCOS

INTRODUCTION

Women in their reproductive age are often impacted by polycystic ovary syndrome (PCOS), a widespread endocrine condition.[1]Hyperprolactinemia (HPRL) is an endocrine disorder in which the bloodstream contains excessive amounts of prolactin (PRL), as seen in its distinguishing feature. PRL is a hormone responsible for lactation, breast development, and other actions needed for normal physiology.[2]

On the other hand, chronic inflammation is a common feature in both PCOS and HPRL. In PCOS, elevated levels of inflammation markers, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), have been observed.[3,4] Similarly, HPRL has been characterized by elevated levels of inflammatory markers.[2] The relationship between HPRL and PCOS may be mediated by several interconnected mechanisms, including inflammation, immune system modulation, insulin resistance and gut microbiota alterations.[5]

Given the evidence connecting prolactin, inflammation, and PCOS, it is important to understand their interrelationships. Elevated PRL levels could contribute to chronic inflammation by promoting immune cell activation or cytokine release from adipose tissue.[6] Therefore, it is plausible that there may be a relationship between PRL levels and markers of inflammation in PCOS patients. The mechanisms underlying this association remain unclear, but investigating their potential interplay could provide new perspectives into the development of this multifaceted disorder.

Some studies have found higher levels of inflammatory markers like CRP, TNF-alpha, and IL-6 in women with HPRL and PCOS compared to controls.[7,8] Given the evidence connecting prolactin, inflammation, and PCOS, it is important to understand their interrelationships.Elevated PRL levels could contribute to chronic inflammation by promoting immune cell activation or cytokine release from adipose tissue.[9,10] Therefore, it is plausible that there may be a relationship between PRL levels and markers of inflammation in PCOS patients.

The mechanisms underlying this association remain unclear, but investigating their potential interplay could provide new perspectives into the development of this multifaceted disorder.In this study, we focus on the inflammatory effect of prolactin and its captivating dimension to the research. We aim to shed light on the potential interplay between PRL levels and markers of inflammation in PCOS patients, with a particular focus on the inflammatory effect of PRL. By investigating this relationship, we hope to provide new insights into the development of PCOS and its potential clinical implications.

METHODS

This retrospective study was conducted between June 2021 and December 2022 at Bezmialem Vakıf University Hospital Gynecology and Obstetric Department. The study was carried out with the permission of Bezmialem Vakıf University Hospital Ethics Committee (Date: 07.06.2023, Decision No:2023/190). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 120 patients aged 18-30 who applied to our outpatient clinics with menstrual irregularity with PCOS, and a control group with similar age and body mass index (BMI) were included in the study. For determining the eligibility criteria for the study, based on the history, physical examination, and ultrasonography evaluation taken from the patients who applied to the outpatient clinic between the specified dates, the diagnosis of PCOS was made on the condition of having at least two of the 2003 Rotterdam Consensus criteria.[11]

Inclusion criteria in the study group were: (1) women between the ages of 18-30 who cannot have children despite wanting a child for at least one year; (2) those diagnosed with PCOS, provided that they have at least two of the 2003 Rotterdam Consensus criteria; (3) those who are not diagnosed with diabetes mellitus, impaired glucose tolerance, thyroid dysfunction, HPRL, and hypercortisolism; (4) women were not given oral contraceptives or any medication known to alter insulin metabolism, lipid, or hormones in the last 90 days; (5) non-smokers.

Criteria for exclusion from the study group were: (1) Smokers; (2) women with diabetes, hypertension, and endocrinopathy; (3) individuals who have consumed medication for the treatment of PCOS, and those who have taken oral contraceptives within the past three months., those who use drugs that increase insulin sensitivity or those who use drugs for hyperlipidemia; (4) patients taking vitamin B12 supplements were excluded due to the effect of B12 on reducing homocysteine, which could confound results. In this study, four groups are considered.

Group I is defined as follows: women with PCOS with HPRL.

Group II is defined as follows: women with PCOS with normal PRL.

Group III is defined as follows: healthy women with HPRL.

Group IV is defined as follows: healthy women with normal PRL.

Among the patients who applied to our routine obstetrics and gynecology outpatient clinic with menstrual irregularity and a desire to have children, we examined the patients on the third day of their menstrual cycle. Levels of inflammatory markers including CRP, TNF-α, and IL-6 were examined. The data of PCOS patients and the control group were analyzed retrospectively.

Statistical Analysis

The sample size of 120 was determined based on a power analysis indicating this would provide 80% power to detect significant differences between groups. Statistical analysis was conducted using SPSS version 26**.** Normality of data was assessed using the Shapiro-Wilk test. Differences between groups were analyzed using independent t-tests for normal data and Mann-Whitney U tests for non-normal data. Associations were examined using Spearman correlation coefficients. $P<0.05$ will be considered statistically significant.

RESULTS

This study included 120 age-matched (24.83±2.27) and body mass index (BMI)-matched (23.93±1.09) women. Table 1 shows the relationship between case and control groups regarding inflammatory markers. In the following, inflammatory markers of women with PCOS in two groups (HPRL and normal PRL) were examined. As stated in Table 1, an Independent t-test showed a significant statistical association between group I and II regarding Hemoglobin (Hb) ($p<0.05$). Hb in PCOS patients was significantly elevated in the normal PRL group. As stated in Table 1, a Mann-Whitney U test found a statistically significant association between groups I and II regardingred cell distribution width (RDW-SD) and mean platelet volume (MPV) levels ($p<0.05$). There was a significant reduction in these parameters in the normal PRL group. There was a significant association between group I and II regarding platelets ($p<0.05$).

The results show a statistically significant difference in PRL levels between PCOS patients and controls, with PCOS patients having higher levels of PRL. However, there is no statistically significant difference in CRP levels between the PCOS and control groups. Hb levels are significantly lower in PCOS patients with HPRL compared to controls with normal PRL levels. RDW-SD is significantly higher in PCOS patients with HPRL compared to controls with normal PRL levels. Platelet levels are significantly lower in

Table 1. The relationship between case and control groups in terms of inflammatory markers

	PCOS (n=60) Mean±SD			Controls (n=60) Mean±SD			
Parameter	Hyper-PRL (Group I) n=30	Normal-PRL (Group II) n=30	p	Hyper-PRL (Group III) n=30	Normal-PRL (Group IV) n=30	p	p
PRL	31.13±2.62	14.87±2.92	**<0.001**	31.4±2.82	14.77±3.24	**<0.001**	0.759
CRP	2.15±1.61	1.68±1.19	0.432	2.07±1.73	1.27±0.83	0.086	0.782
Hb	12.31±1.39	13.16±0.99	**0.008**	12.18±1.28	12.84±1.21	0.045	0.695
RDW-SD	35.28±3.08	33.53±3.5	**<0.001**	34.75±2.6	34.02±2.91	**0.041**	0.589
Platelet	241433.33±56159.68	288300±69559.77	**0.010**	242133.33±56617.13	278566.67±67133.26	**0.041**	0.988
MPV	9.77±1.55	9±2.09	**0.019**	9.63±1.61	9.65±1.18	0.336	0.711
PDW	13.39±3.48	12.39±4.53	0.105	13.61±3.69	11.64±3.06	**0.008**	0.900

*** SD, standard deviation; PLR, platelet/lymphocyte ratio; CRP, C-reactive protein; Hb, Hemoglobin; RDW-SD, a red cell distribution width; MPV, mean platelet volume; PDW, platelet distribution width;. Parametric values were expressed as means ± SD.**

controls with HPRL compared to controls with normal PRL levels. MPV is significantly higher in PCOS patients with HPRL compared to controls with normal PRL levels. platelet distribution width (PDW) is significantly higher in controls with HPRL compared to PCOS patients with normal PRL levels.

In PCOS patients, there is a statistically significant positive correlation between PRL levels and RDW-SD (r=0.352, p=0.006). There is a statistically significant negative correlation between PRL levels and Hb (r=-0.313, p=0.015). There is a statistically significant negative correlation between PRL levels and platelet count (r=-0.293, p=0.023). There is a statistically significant positive correlation between PRL levels and MPV (r=0.300, p=0.020). There is a statistically significant positive correlation between PRL levels and PDW (r=0.287, p=0.026).

In controls, there is no statistically significant correlation between PRL levels and any of the inflammatory markers.

Based on these results, we can conclude that in PCOS patients, higher PRL levels are associated with increased RDW-SD, decreased Hb levels, decreased platelet count, and increased MPV and PDW. However, there is no significant correlation between PRL levels and inflammatory markers in the control group.

It is important to note that these results are based on the correlation analysis and do not establish a causal relationship between PRL levels and inflammatory markers. Further research is needed to understand these associations underlying mechanisms and potential clinical implications.

Table 2. Correlation between PRL and Inflammatory Markers

	PCOS		Controls		
Parameter	r	p-values	Parameter	r	p-values
AMH (ng/ml)	-0.057	0.668	AMH (ng/ml)	-0.050	0.704
FSH (mIU/ml)	0.047	0.719	FSH (mIU/ml)	-0.110	0.404
LH (mIU/ml)	-0.083	0.531	LH (mIU/ml)	0.011	0.936
E2 (pg/ml)	-0.013	0.923	E2 (pg/ml)	0.046	0.730
TSH (mIU/l)	-0.066	0.615	TSH (mIU/l)	0.116	0.376
Free T4 (pmol/l)	-0.090	0.493	Free T4 (pmol/l)	0.011	0.934
CRP (mg/dl)	0.082	0.536	CRP (mg/dl)	0.199	0.128
Leukocyte	0.205	0.115	Leukocyte	0.006	0.964
Neutrophil	-0.063	0.633	Neutrophil	-0.017	0.900
Lymphocyte	-0.126	0.339	Lymphocyte	0.103	0.435
Monocyte	-0.037	0.777	Monocyte	0.004	0.974
Basophil	-0.131	0.317	Basophil	0.021	0.874
Hb	-.313*	**0.015**	Hemoglobin	-0.176	0.178
RDW-SD	.352**	**0.006**	RDW-SD	0.211	0.106
Platelet	-.293*	**0.023**	Platelet	-.304*	**0.018**
MPV	.300*	**0.020**	MPV	0.076	0.562
PDW	0.147	0.261	PDW	.287*	**0.026**
NLO	0.072	0.583	NLO	-.043	0.746
LMO	-0.079	0.546	LMO	0.038	0.776
TLO	-0.013	0.920	TLO	-0.308	**0.017**

*p<0.05: statistically significant.
*AMH, Anti-Müllerian hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol; TSH, thyroid stimulating hormone; Free T4, free thyroxin; CRP, C-reactive protein; Hb, Hemoglobin; RDW-SD, a red cell distribution width; MPV, mean platelet volume; PDW, platelet distribution width; NLR,neutrophil/lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet/lymphocyte ratio. Parametric values were expressed as means ± SD. SD, standard deviation.

DISCUSSION

The present study aimed to investigate the relationship between PRL levels and inflammatory markers in PCOS patients and controls. Results showed that PCOS patients had significantly higher levels of PRL than controls. However, there was no significant difference in creative protein (CRP) levels between the two groups. Hb levels were significantly lower in PCOS patients with HPRL compared to controls with normal PRL levels. RDW-SD was significantly higher in PCOS patients with HPRL compared to controls with normal PRL levels. Platelet levels were significantly lower in controls with HPRL compared to controls with normal PRL levels. MPV was significantly higher in PCOS patients with HPRL compared to controls with normal PRL levels. PDW was significantly higher in controls with HPRL compared to PCOS patients with normal PRL levels.

The results of this study are consistent with previous research that has shown that women with PCOS have elevated levels of inflammatory markers such as CRP.[12] However, our study did not find a significant difference in CRP levels between PCOS patients and controls. This inconsistency may be due to differences in the study population, sample size, and measurement methods. In addition, our study found that Hb levels were significantly lower in PCOS patients with HPRL compared to controls with normal PRL levels. This finding is consistent with previous research that has shown that PCOS patients have higher Hb levels than controls.[13] The reason for this association is not clear, but it may be related to the hormonal imbalances that occur in PCOS.

The correlation between PRL levels and various inflammatory markers in PCOS patients and controls in our study found that in PCOS patients, higher PRL levels were associated with increased RDW-SD, decreased Hb levels, decreased platelet count, and increased MPV and PDW. However, there was no significant correlation between PRL levels and inflammatory markers in the control group. These results suggest that higher PRL levels may be associated with increased inflammation in PCOS patients.

Our findings are consistent with previous research that has shown a link between PRL levels and platelet activation in women with PCOS.[14] The present study found that higher PRL levels were associated with increased MPV and PDW in PCOS patients. This finding is consistent with previous research that has shown that women with PCOS have higher MPV levels than women without PCOS.[15] The present study also found that higher PRL levels were associated with decreased platelet count in PCOS patients. This finding is consistent with previous research that has shown that women with PCOS have lower platelet counts than women without PCOS.[16]

The hypothesis of this study was that higher PRL levels would be associated with increased inflammatory markers in PCOS patients compared to controls. The results of this study partially support the hypothesis that higher PRL levels are associated with increased inflammatory markers in PCOS patients. Specifically, higher PRL levels were associated with increased RDW-SD, decreased Hb levels, decreased platelet count, and increased MPV and PDW in PCOS patients. However, there was no significant correlation between PRL levels and inflammatory markers in the control group.

Similar studies have shown inconsistent results regarding the association between PRL levels and inflammatory markers in PCOS patients. For example, a study by Rudnicka et al.[12] found increased serum CRP in women with PCOS compared to healthy controls. However, our study did not find a significant difference in CRP levels between PCOS patients and controls. Another study by Saei Ghare Nazet al.[17] found a link between PRL levels and platelet activation in women with PCOSwhich is consistent with our finding that higher PRL levels were associated with decreased platelet count in PCOS patients.

The findings of this study have several implications for the understanding and management of PCOS and its associated inflammatory markers.Higher PRL levels may be associated with increased inflammation in PCOS patients. Specifically, higher PRL levels were associated with increased RDW-SD, decreased Hb levels, decreased platelet count, and increased MPV and PDW in PCOS patients. The lack of significant correlation between PRL levels and inflammatory markers in the control group suggests that the observed associations are specific to PCOS patients. This highlights the importance of considering the unique pathophysiology of PCOS when investigating the relationship between hormonal imbalances and inflammatory markers.

The significant differences in Hb, RDW-SD, platelet count, MPV, and PDW between PCOS patients and controls suggest that these inflammatory markers may be useful in the diagnosis and management of PCOS. Further research is needed to determine the clinical implications of these findings.

The lack of significant difference in CRP levels between PCOS patients and controls suggests that CRP may not be a reliable marker of inflammation in PCOS. Other inflammatory markers, such as RDW-SD, MPV, and PDW, may be more useful in this context. The significant correlation between PRL levels and RDW-SD, MPV, and PDW in PCOS patients suggests that these markers may be useful in monitoring the effects of PRL-lowering therapies in PCOS patients.

Overall, these findings suggest that PRL may play a role in the inflammatory processes associated with PCOS, and that inflammatory markers such as RDW-SD, MPV, and PDW may be useful in the diagnosis and management of PCOS. Further research is needed to determine the clinical implications of these findings and to investigate the underlying mechanisms of the observed associations.

Limitations of the Study

The present study has several limitations that should be considered when interpreting the results. Firstly, the retrospective design of the study may have introduced bias into the data collection process. This design relies on data that has already been collected, which may limit the ability to control for confounding variables. Secondly, the sample size of the study is relatively small, with only 60 PCOS patients and 60 controls. This may limit the generalizability of the findings and may reduce the statistical power of the study.

Thirdly, the study only measured a limited number of inflammatory markers, including CRP, Hb, RDW-SD, MPV, and PDW. Other markers, such as interleukins and tumor necrosis factor, may also be relevant to the inflammatory processes associated with PCOS. Therefore, the findings

of this study may not be representative of the full range of inflammatory markers that are associated with PCOS.

Finally, PRL levels can vary widely depending on a variety of factors, including stress, exercise, and medication use. This variability may limit the ability to draw firm conclusions about the relationship between PRL levels and inflammatory markers. Therefore, further research is needed to confirm the findings of this study and to investigate the underlying mechanisms of the observed associations.

Despite these limitations, the findings of this study have important implications for the understanding and management of PCOS and its associated inflammatory markers. The study found that higher PRL levels were associated with increased inflammation in PCOS patients, and that inflammatory markers such as RDW-SD, MPV, and PDW may be useful in the diagnosis and management of PCOS. However, further research is needed to confirm these findings and to investigate the underlying mechanisms of the observed associations.

CONCLUSION

Our study found that higher PRL levels were associated with increased inflammation in PCOS patients. Specifically, higher PRL levels were associated with increased RDW-SD, decreased Hb levels, decreased platelet count, and increased MPV and PDW in PCOS patients. These findings suggest that PRL may play a role in the development of inflammation in PCOS patients. However, further research is needed to understand the underlying mechanisms and potential clinical implications of these associations.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bezmialem Vakıf University Hospital Ethics Committee (Date: 07.06.2023, Decision No:2023/190).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Murat Önal

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Original Article

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The role of gestational weight gain rate in the development of maternal iron deficiency anaemia

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ABSTRACT

Aims: Our aim is to analyze the effect of weight gain rates on the development of anaemia in a homogeneous group of pregnant women taking similar nutritional supplements in our own society and to emphasize the importance of weight control based on this hypothesis.

Methods: The study was conducted retrospectively with 127 pregnant women between 20 and 40 years old. Pregnant women in normal weight and having body mass index (BMI) between 18.5 and 24.9 were included in the study. These women were divided into two groups according to the amount of weight they gained during pregnancy: those who weighed less than 11 kg and those who gained 11 kg or more. Ages of patients, number of pregnancies and births, 1st and 3rd trimester weights, 1st and 3rd trimester weight differences, 1st and 3rd trimester hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV) measurements were recorded. The correlation of changes between weight gain and blood parameters was evaluated.

Results: No statistically significant change was observed between the 1st and 3rd trimester Hgb and Hct averages of pregnant women who gained less than 11 kg during pregnancy. 3rd Trimester Hb, Hct averages of the pregnant group who gained 11 kg or more were found to be statistically significantly lower than the outset Hb, Hct averages (p=0.001, p=0.001). No statistically significant difference was observed between the 1st Trimester and 3rd Trimester MCV averages of the <11 kg difference and >11 kg difference groups (p=0.271, p=0.183). No statistically significant difference was observed between the 1st trimester ferritin averages of the <11 kg difference and >11 kg difference groups (p=0.055). 3rd trimester ferritin averages of the >11 kg difference group were found to be statistically significantly lower than the <11 kg difference group (p=0.016).

Conclusion: As a result of our study, we can say that rapid weight gain during pregnancy deepens anaemia. Randomized studies continue to be the best source of evidence in testing hypotheses mentioning that early use of iron supplements and strengthening weight control may reduce the risk of iron deficiency anemia.

Keywords: Gestational weight gain rate, iron deficiency, anaemia, pregnancy, BMI.

INTRODUCTION

Obesity shows a significant increase in worldwide. It is estimated that more than 21% of women shall be obese and 9% shall be severely obese in 2025.[1] On the other hand, the incidence of maternal obesity also increases and this situation becomes one of the most important health problems during pregnancy. Excessive weight gain causes various complications such as gestational hypertension, diabetes, anaemia, preeclampsia, premature birth and spontaneous abortus by affecting both the mother and the baby.[2] The risks in babies are babies who are large for gestational age, macrosomia, and overweight or obesity in childhood. Today, approximately 50% of women exceed their weight gain goals in terms of weight gain during pregnancy.

Anaemia is a comorbidity which is observed frequently during pregnancy. It is estimated that the prevalence of anaemia of pregnancy 38%, in worldwide and it means that 32 million pregnant women are affected.[3] More than 50% of these appear to be the result of iron deficiency.[3,4] Iron deficiency anaemia during pregnancy is preventable causes that can lead to serious negative consequences such as premature rupture of membranes, puerperal infection, fetal growth retardation, fetal hypoxia and premature birth.[3,5] Previous studies have identified several potential risk factors for iron deficiency anaemia, such as poor nutritional status, multiple pregnancies, poor socioeconomic status, age over 30 years, multiparity, and frequent interbirth interval.[6,7] However, the potential effect of body weight on iron deficiency anaemia has not been adequately analyzed. Our aim is to analyze the

effect of weight gain rates on the development of anaemia in a homogeneous group of pregnant women taking similar nutritional supplements in our own society and to emphasize the importance of weight control based on this hypothesis.

METHODS

The study was carried out with the permission of Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Researches Ethics Committee (Date: 04.09.2023, Decision No: 2023-17). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki and documented declared permission was received from all women.

The study was conducted retrospectively with 127 pregnant women between 20 and 40 years old who were followed up in the same center due to pregnancy between January 2021 and May 2023. The pregnant women who smoke, have twin and multiple pregnancies, have a bleeding condition that complicates their pregnancies (placental abruption, placenta previa, etc.), have chronic disease anaemia, and are thalassemia carriers; have polycythemiavera, megaloblastic anaemia and chronic blood disease diagnosis, or who have received or are receiving bone marrow suppressant treatment were not included in the study.

Pregnant women in normal weight and having body mass index (BMI) between 18.5 and 24.9 were included in the study. These women were divided into two groups according to the amount of weight they gained during pregnancy: those who weighed less than 11 kg and those who gained 11 kg or more.

Ages of patients, number of pregnancies and births, 1. and 3rd trimester weights, 1st and 3rd trimester weight differences, 1st and 3rd trimester haemoglobin (Hb), haematocrit (Hct), mean corpuscular volume (MCV) measurements were recorded. The correlation of changes between weight gain and blood parameters was evaluated.

All patients were selected homogeneously from patients who used 100 mg elemental iron equally after the first trimester until birth.

Statistical Analysis

In this study, statistical analyses were performed with the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program.

In the evaluation of the data, in addition to descriptive statistical methods (mean, standard deviation, median, interquartile range), the distribution of the variables was examined with the Shapiro-Wilk normality test, paired t test was used in the 1st Trimester-3rd trimester comparisons of variables showing normal distribution and independent t test was used in the comparison of paired groups, Wilcoxon test was used for comparisons between the 1st Trimester and 3rd Trimester of variables not showing normal distribution, Mann Whitney U test was used for comparison of paired groups, and chi-square test was used for comparisons of qualitative data. The results were evaluated at the significance level of $p<0.05$.

RESULTS

127 pregnant women were included in the study. Age, weight (kg), gravida, parity status, total weight gain in the 3rd trimester, 1st and 3rd trimester Hb, Hct, MCV and ferritin values of these pregnant women are given in Table 1. The weight of the patients when the first pregnancy was diagnosed and the weight measured at the time of birth in the 3rd trimester were recorded, and the difference was calculated as total weight gain. Accordingly, the amount of weight that patients should gain during pregnancy is considered to be approximately 10-12 kg. The average weight gain of pregnant women was calculated as an average of 11 kg during pregnancy and they were divided into two groups: those who gained less than 11 kg and those who gained 11 kg or more.

Table 1 shows that the initial weight of the patients was between 52-72 kg and the average for the whole group was 62.39±9.38 kg. The initial average weight of those who weighed less than 11 kg at the end of pregnancy was 63.52±9.21 kg, and the initial average weight of those who gained 11 kg or more at the end of pregnancy was 61.41±9.48 kg, and no statistically significant difference was observed ($p=0.207$). No statistically significant difference was observed between the 3rd Trimester weight averages ($p=0.058$). The mean age of the >11 kg difference group was found to be statistically significantly lower than the <11 kg difference group ($p=0.005$). 3rd Trimester weight average of the >11 kg difference group was found to be statistically significantly higher than the initial weight average ($p=0.0001$).

No statistically significant difference was observed between the 1st Trimester Hb averages of the <11 kg Difference and >11 kg Difference groups ($p=0.123$). 3rd Trimester Hb averages of the >11 kg Difference group were found to be statistically significantly lower than the <11 kg Difference group ($p=0.008$).

3rd Trimester Hb averages of the >11 kg Difference group were found to be statistically significantly lower than the initial Hb averages ($p= 0.001$)

No statistically significant difference was observed between the 1st Trimester Hct averages of the <11 kg difference and >11 kg difference groups ($p=0.753$) (Table I).

3rd Trimester Hct averages of the >11 kg Difference group were found to be statistically significantly lower than the <11 kg difference group ($p=0.033$) (Table I).

No statistically significant change was observed between the 1st Trimester and 3rd Trimester Hct averages of the <11 kg Difference group ($p=0.466$).

3rd Trimester Hct averages of the >11 kg Difference group were found to be statistically significantly lower than the initial Hct averages ($p=0.001$).

No statistically significant difference was observed between the 1st Trimester and 3rd Trimester MCV averages of the <11 kg difference and >11 kg difference groups ($p=0.271$, $p=0.183$) .

Table 1: Characteristic features of patients

			Whole Group	<11 kg Difference	>11 kg Difference	p
Age		Mean±SD	33.75±3.89	34.78±4.19	32.85±3.38	0.005*
Gravida		Mean±SD	1.45±0.59	1.51±0.68	1.4±0.49	
		Median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	0.519†
Parity		Mean±SD	1.08±0.39	1.15±0.54	1±0	0.161†
		Median (IQR)	1 (1-1)	1 (1-1)	1 (1-1)	
Weight (kg)	Initial	Mean±SD	62.39±9.38	63.52±9.21	61.41±9.48	0.207*
	3.Trimester	Mean±SD	75.07±9.81	73.30±9.61	76.60±9.79	0.058*
	p**			0.0001	0.0001	
Hb (g/dL)	1.Trimester	Mean±SD	12.26±0.88	12.13±0.94	12.37±0.81	0.123*
	3.Trimester	Mean±SD	11.66±1.24	11.97±1.18	11.39±1.24	0.008*
	p**			0.349	0.001	
Hct (%)	1.Trimester	Mean±SD	35.86±2.78	35.77±2.96	35.93±2.63	0.753*
	3.Trimester	Mean±SD	35.34±5.53	35.63±3.42	34.37±3.34	0.033*
	p**			0.466	0.001	
MCV(fL)	1.Trimester	Mean±SD	88.44±4.78	88.94±5.00	88.00±4.58	0.271*
	3.Trimester	Mean±SD	88.70±6.82	89.57±6.32	87.95±7.17	0.183*
	p**			0.350	0.948	
Ferritin (ng/mL)	1st Trimester	Mean±SD	48.17±21.97	53.27±25.59	43.75±17.27	
		Median (IQR)	43 (29-68)	45 (29-76)	41 (29-57)	0.055†
	3rd Trimester	Mean±SD	21.49±11.33	24.14±11.61	19.19±10.63	
		Median (IQR)	21 (11-31)	23 (13-31)	17 (11-27)	0.016†
	p‡			0.0001	0.0001	

*Independent t test, **Paired t test †Mann Whitney U test ‡Wilcoxon test, Hb (Hemoglobin) g/dL, Hct (Hematocrit) %, MCV (mean corpuscular volume) fL

No statistically significant change was observed between the 1st Trimester and 3rd Trimester MCV averages of the <11 kg difference group (p=0.350).

No statistically significant change was observed between the 1st Trimester and 3rd Trimester MCV averages of the >11 kg difference group (p=0.948).

No statistically significant difference was observed between the 1st Trimester ferritin averages of the <11 kg Difference and >11 kg difference groups (p=0.055).

3rd Trimester ferritin averages of the >11 kg Difference group were found to be statistically significantly lower than the <11 kg difference group (p=0.016).

Table 2 shows that 1st Trimester-3rd Trimester Hb difference averages of the >11 kg difference group were found to be statistically significantly higher than the <11 kg difference group (p=0.0001).

The 1st Trimester-3rd Trimester Hct difference averages of the >11 kg Difference group were found to be statistically significantly higher than the <11 kg difference group (p=0.018).

No statistically significant difference was observed between the 1st Trimester-3rd Trimester MCV difference averages of the <11 kg difference and >11 kg difference groups (p=0.414).

No statistically significant difference was observed between the 1st Trimester-3rd Trimester ferritin difference averages of the <11 kg difference and >11 kg difference groups (p=0.378).

Table 2: Differences between 1st and 3rd trimester Hgb, Hct, MCV and Ferritin values according to the amount of weight gained by pregnant women

1st Trimester-3rd Trimester Difference		Whole Group	<11kg Difference	>11kg Difference	p†
Hgb (g/dL)	Mean±SD	0.6±1.28	0.16±1.3	0.98±1.14	
	Median (IQR)	0.6 (-0.1-1.5)	0.2 (-1-0.9)	1.05 (0.3-1.7)	0.0001
Hct (%)	Mean±SD	0.52±5.47	0.12±3.62	1.56±3.14	
	Median (IQR)	1.5 (-1.5-2.8)	0.1 (-2.2-2.4)	2.15 (-0.05-3.6)	0.018
MCV (fL)	Mean±SD	-0.31±6.45	-0.73±5.91	0.05±6.9	
	Median (IQR)	-1 (-4.68-5)	-1.55 (-5.05-2.15)	-0.8 (-4.08-5.6)	0.414
Ferritin (ng/mL)	Mean±SD	26.68±16.23	29.13±18.97	24.56±13.2	
	Median (IQR)	23 (15-42)	25 (13-44)	21.71 (15-35)	0.378

† Mann Whitney U test, Hb (Hemoglobin) g/dL, Hct (Hematocrit) %, MCV (mean corpuscular volume) fL

Table 3 and figure 1 shows that apositive, statistically significant correlation was observed between the Start-3rd Trimester weight difference values and the 1st-Trimester-3rd Trimester hemoglobin difference values (r=0.425 p=0.0001). A positive, statistically significant correlation was observed between the Baseline-3rd Trimester weight difference values and the 1st Trimester-3rd Trimester hematocrit difference values (r=0.224 p=0.011).

Table 3: The relationship between 1st Trimester-3rd Trimester weight differences and Hb, Hct, MCV and ferritin differences

1st Trimester-3rd Trimester Difference		Weight Difference
Hb	r	0.425
	p	0.0001
Hct	r	0.224
	p	0.011
MCV	r	0.304
	p	0.001
Ferritin	r	-0.047
	p	0.600

Pearson Correlation test, Hb (Hemoglobin) g/dL, Hct (Hematocrit) %, MCV (mean corpuscular volume) fL

A positive, statistically significant correlation was observed between the initial-3rd Trimester weight difference values and the 1st Trimester-3rd Trimester MCV difference values (r=0.304 p=0.001).

No statistically significant correlation was observed between the initial-3rd Trimester weight difference values and the 1st-Trimester-3rd Trimester ferritin difference values (r=-0.047 p=0.600).

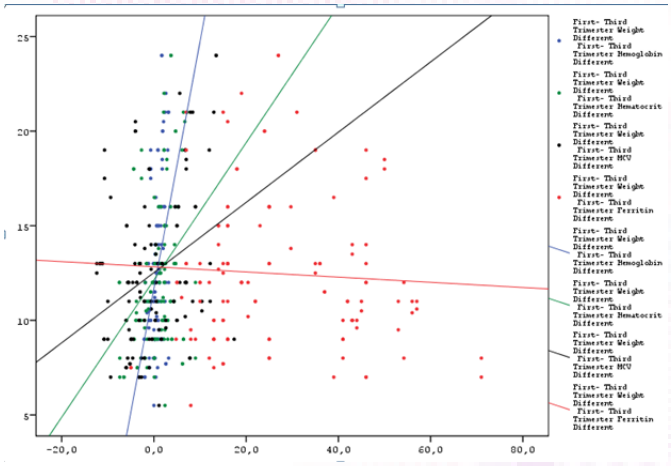

Figure 1: 1st and 3rd trimesters of all pregnant women. Change in weight, Hb, Hct, MCV and Ferritin values in the trimester.

DISCUSSION

Maternal weight indicators, such as pre-pregnancy BMI and gestational weight gain, represent important measures of maternal metabolism and nutritional status. It is observed that the risks of iron deficiency and iron deficiency anemia (IDA) increase among pregnant women with obesity in developed countries,[8,9] but the risk of iron deficiency anaemia appears to be higher among low birth weight women in developing countries.[10,11] A woman's inadequate nutrition before pregnancy, insufficient calorie and protein intake, as well as lack of nutrients such as iron stored in the body, and low socio-economic status may be responsible for iron deficiency anaemia in underweight women. Meanwhile, it is well known that women with higher socio-economic status are more likely to control their body weight better.[12] In our study, unlike these studies, the effect of excess weight gain during pregnancy on anaemia in women with similar BMI was evaluated.

Weight gain in pregnant women is regulated according to BMI, based on the guideline accepted in 2009. According to this; weight gain should be 12.5-18 kg in those with low BMI (<18.5), should be 11.5-16 kg in those with normal BMI (18.5-24.9), 6.8-11,3 kg in those with overweight BMI (25-29.9) and should be 5-9 kg for pregnant women who are obese (BMI>30).[13] Our study group consisted of pregnant women with normal BMI (18.5 to 24.9). Accordingly, the groups were divided into 2 by taking 11 kg as basis. Anaemia was evaluated in those who weighed less than 11 kg and those who weighed 11 kg or more. In our study, while there was no difference between the Hb and Hct values of all our patients at the beginning of pregnancy, it was revealed that the risk of developing anaemia increased in those whose weight gain was 11 kg or more. Although all pregnant women were given 100 mg elemental iron supplement prophylactically after the 3rd month, ferritin values were found significantly lower than those who gained 11 kg or more in the 3rd trimester of pregnant women. No significant change was detected in the MCV value. The lack of change in MCV may be due to the iron supplements given. However, low ferritin may be attributed to the mother's rapid weight gain and iron insufficiency. It is known that there is increased IL-6 release, especially in patients with abdominal obesity.[14] Increased IL-6-related hepcidin production may also hinder the effective use of iron by the bone marrow.[14] This situation may have contributed to the formation of anaemia in these pregnant women. It was observed that iron deficiency continued in women who gained 11 kilos or more despite the iron supplements they used during pregnancy. Iron deficiency was defined as <15 µg/L serum concentration of ferritin level in most studies, as <12 µg/L serum concentration in some studies, and as <10 µg/L serum concentration in a few studies.[15] In our study, serum ferritin concentrations <13 µg/L were considered iron deficiency. The aetiologies and types of IDA development during pregnancy may possibly vary.[10] In addition to the development of IL-6-related anaemia, nutritional or socioeconomic reasons may also cause the development of anaemia. To understand how socioeconomic and nutritional factors affect gestational IDA among different women may help prenatal caregivers, midwives, and dietitians develop effective intervention programs to prevent gestational IDA.

Consequently, our study showed that women with normal BMI have a higher risk of gestational anaemia and IDA when weight gain increases, and this situation clearly emphasizes that rapid weight gain is undesirable during pregnancy. Weight control should be strengthened among pregnant women. Additionally, detailed studies are needed to see how it affects the weight of babies of these pregnant women.

Limitation of the study

Despite obtaining valuable data in our study, it is important to acknowledge the limitations and areas for improvement. First of all, the study was conducted

retrospectively on a relatively small number of patients. To conduct prospective studies with larger participation shall provide more reliable research results. The fact that IL-6 level, which is known to be important in the pathogenesis of anaemia, could not be studied, should also be considered among the limitations.

CONCLUSION

As a result of our study, we can say that rapid weight gain during pregnancy deepens anaemia. Randomized studies are needed in testing the hypotheses arguing that early use of iron supplements and strengthening weight control may reduce the risk of IDA.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Researches Ethics Committee (Date: 04.09.2023, Decision No: 2023-17).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Comparison of clinical and biochemical parameters in the ovulatory and anovulatory phenotypes of polycystic ovary syndrome

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ABSTRACT

Aims: We aimed to compare the clinical and the biochemical features of the ovulatory versus anovulatory phenotypes of polycystic ovary syndrome (PCOS).

Methods: This is a retrospective controlled trial conducted among the women who applied to the İstanbul Liv Vadi Hospital between 2021 and 2023 August and diagnosed as PCOS. PCOS patients (n=290) were diagnosed according to the Rotterdam 2003consensus criteria. Women's clinical and biochemical parameters such as age, height, weight, body mass index (BMI), waist, hip, waist/hip ratio (WHR), fasting blood sugar (FBS), insulin, homeostatic model-assessment-insulin resistance (HOMA-IR), antimullerian hormone (AMH), follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) total cholesterol,triglyceride, dehydroepiandrosterone (DHEAS), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) of participants were compared between ovulatory and anovulatory phenotypes.

Results: The findings of the study did not demonstrate a statistically significant correlation between ovulatory and anovulatory phenotypes in relation to various factors, including height, weight, BMI, waist circumference, hip circumference, WHR, insulin levels, HOMA-IR, AMH, FSH, E2, TSH, total cholesterol, testosterone, free testosterone, DHEAS, LDL and cholesterol (p-value>0.05). A statistically significant difference was observed between the groups in terms of age, FBS, BMI, LH, and HDL levels.

Conclusion: In conclusion, there is no significant difference in PCOS's ovulatory and anovulatory phenotypes in essential parameters such as insulin resistance and BMI.

Keywords: Polycystic ovary syndrome, PCOS phenotypes, insulin resistance, women, ovulatory and anovulatory phenotypes

INTRODUCTION

Being recognized as one of the most common endocrine problems, polycystic ovary syndrome (PCOS) is associated with a high variety of symptomatology.[1,2] Women with PCOS are at increased risk of fertility problems due to anovulation but also may be presented with menstrual disorders, acne, hirsutismus, metabolic problems such as insulin resistance, type 2 diabetes, obesity, high blood pressure, and mental disorders (anxiety, depression, and stress).[3] Longterm medical therapy, diet and phsyical activity regulations, managing metabolic diseases, arranging regular periods and achieving fertility goals are the well know targets in controlling the complexity of this debilitating endocrine problem.[4] The prevalence of PCOS ranges from 5-13% in women of reproductive age, and approximately 75% suffer from infertility due to lack of ovulation.[5]

Almost 30% of all infertility is infertility with no ovulation, and the cause of about 90% of this infertility is PCOS.[6] Controlling this syndrome and its signs and symptoms improves the quality of life in affected women effectively. Many women with PCOS need long-term treatment.[7-9] Commonly available drugs are effective on PCOS, but they have many side effects, and this issue has made non-pharmacological treatment strategies to be investigated and studied more.[10,11] The cause of PCOS is not fully understood. However, it seems to have a genetic basis, and fat plays a role in the pathogenesis or other factors in the disease. Identifying risk factors and factors affecting this disease can help provide more effective treatments.[12]

Based on the Rotterdam 2003 consensus, PCOS is usually represented by ovulatory dysfunction that results in oligo

or amenorrhea. Most symptoms will also rely on whether PCOS is explored in an internal gynecology, dermatology, or medicine background.[13] Women with PCOS often find out about their disease in infertility clinics. These patients have had infertility problems for years due to the anovulation. These anovulatory women seem to have a different phenotype than ovulatory women with PCOS, including clinical, metabolic, and biochemical parameter differences.[14]

Whether these two phenotypes represent a similar spectrum of conditions in terms of clinical and biochemical parameters is still ambiguous. More work must be done to study the different clinical and biochemical parameters in the ovulatory and anovulatory phenotypes. This study aims to compare the differences among the clinical and biochemical parameters profile of different PCOS phenotypes. This comparison may help understand PCOS phenotype characteristics.

METHODS

The study was carried out with the permission of İstinye University Ethics Committee (Date: 22.09.2023, Decision no: 2023/09). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki and documented declared permission was received from all women.

The examination sample consisted of women witholigomenorrhea or amenorrhea, who visited İstanbul Liv Vadi Hospital between Aug 2021 and August 2023. In this study, women who had been analyzed with WHO anovulation and who fulfilled the diagnostic standards of PCOS employed the Rotterdam 2003 consensus.

Women who had a diagnosis of Cushing syndrome, androgen-secreting neoplasia, congenital adrenal hyperplasia, any malignancy and women with a history of oral glucocorticoid or oral contraceptive medication and who were already on antidiabetic treatment were excluded from the study. The inclusion criteria for the study are listed as follows: Women who were between the ages of 18-40, being diagnosed with PCOS, menstrual irregularity, hirsutism, acne, polycystic ovarian morphology, and who had provided the complete demographic and laboratory data.

This study divided women with PCOS into two groups: anovulatory (n=180) and ovulatory (n=110). In this study, progesterone measurement processed on the twenty-one day of menstrual cycle was used to divide women into two groups. During previous examinations and treatments, women were diagnosed ovulatory polycystic ovary syndrome (PCOS) on the 21st day of their menstrual cycle or when their randomly checked progesterone levels reached a minimum of 10 nmol/liter.[14,15] The remaining women were classified as anovulatory PCOS.

The participants in the research were subjected to a preliminary examination in the first stage. The next step was to measure height and weight, calculate BMI, and collect information about menstruation. Then, blood samples were taken from the patients and processed on the third day of the menstrual cycle. Serum FBS, insulin, HOMA-IR, AMH, follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2),thyroid-stimulatinghormone (TSH),total cholesterol, triglyceride, Testosterone, freetestosterone, dehydroepiandrosterone (DHEAS), high-density lipoprotein (HDL) and low-density lipoprotein (LDL)" were measured.

Statistical Analysis

The SPSS version 26 was used for statistical analysis. The normality of data was tested by the Shapiro-Wilk test and graphic investigations. Descriptive statistical methods were utilized to assess the data. The comparison of normally distributed quantitative variables between the two groups was performed using the Student's t-test. The Mann-Whitney U test was deployed to approximate the non-normally distributed quantitative variables between the two groups. The Pearson chi-square test was used to compare qualitative data.

To calculate the sample size with the G-Power 3.2 program, difference between two independent proportions was measured based on the Pearson's Chi-Square Test of Association with the power of 80%, effect size of 50%, and 0.25 type 1 error for at least 228 patients.[16]

RESULTS

A total of 290 women with PCOS participated in this study. Table 1 shows the comparison of ovulatory and anovulatory phenotypes in women with PCOS in study parameters.

The mean age and body mass index (BMI) of the women with PCOS were 26.57 years and 28.85 kg/m^2 (SD = 5.59 and 6.09). The mean height and weight of the women with PCOS were 160.86 cm and 74.67 kg (SD=5.7 and 16.54). The mean waist and hip of participants in the study were 87.91 cm and 107.17 kg (SD=14 and 12.42). Table 1 shows explanatory details of investigation variables in total and each group. For study parameters with normal distribution, mean (M), and standard deviation (SD), and for non-normal distribution, median and interquartile range (IQR) were used to show descriptive information.

In order to compare the age of ovulatory and anovulatory phenotypes an independent-samples t-test was conducted. There was a statistically significant association between ovulatory and anovulatory phenotypes in women with PCOS regarding age ($p<0.05$). It indicated that the age of the ovulatory group (M=27.93, SD=5.47) was higher than the anovulatory group (M=25.74, SD=5.51).

As shown in Table 1, there was no statistically significant association between ovulatory and anovulatory phenotypes in women with PCOS regarding height, weight, BMI, waist, hip, and waist/hip ratio ($p>0.05$).

As is shown in Table 1, there was not a statistically significant association between ovulatory and anovulatory phenotypes in women with PCOS in terms of FBS and HOMA-IR ($p>0.05$). There was a statistically significant association between the two groups in women with PCOS in terms of insulin ($p<0.05$). We found that the insulin of the ovulatory group (M=10.1, SD=4.98) was lower than that of the anovulatory group (M=12.24, SD=8.48).

Table 1. The comparison of ovulatory and anovulatory phenotypes in women with PCOS in study parameters (n=290).

Study parameters		Total n=290	Ovulatory n=110	Anovulatory n=180	p-value
Age (years)	Mean±SD	26.57±5.59	27.93±5.47	25.74±5.51	**0.001***
Height (cm)	Mean±SD	160.86±5.7	160.98±6.15	160.79±5.43	0.780*
Weight (kg)	Mean±SD	74.67±16.54	74.42±16.52	74.83±16.59	0.838*
BMI (kg/m²)	Mean±SD	28.85±6.09	28.7±6.04	28.95±6.14	0.740*
Waist (cm)	Mean±SD	87.91±14	88.28±14.93	87.68±13.44	0.725*
Hip (cm)	Mean±SD	107.17±12.42	107.54±13.92	106.95±11.45	0.697*
Waist/Hip ratio	Mean±SD	0.82±0.07	0.82±0.07	0.82±0.07	0.926*
FBS (mg/dL)	Mean±SD	95.95±16.41	96.21±19.74	95.78±14.04	0.830*
Insulin (mL)	Mean±SD	11.43±7.42	10.1±4.98	12.24±8.48	**0.017***
HOMA-IR	Mean±SD	2.87±2.28	2.64±2.33	3.01±2.23	0.059**
AMH (ng/mL)	Mean±SD	5.01±2.31	4.82±2.36	5.13±2.28	0.141**
FSH (mIU/mL)	Mean±SD	6.61±1.64	6.68±1.72	6.57±1.59	0.589*
LH (IU/L)	Mean±SD	10.74±5.15	9.93±5.62	11.24±4.78	**0.037***
E2 (pg/mL)	Mean±SD	58.02±35.21	54.99±33.42	59.87±36.22	0.098**
TSH (mIU/mL)	Mean±SD	2.42±1.98	2.29±1.12	2.49±2.36	0.865**
Testosteron (nmol/L)	Mean±SD	1.29±6.85	0.85±0.67	1.56±8.68	0.245**
FreeTestosteron (pg/ml)	Mean±SD	2.69±1.28	2.5±1.14	2.81±1.35	0.061**
DHEAS	Mean±SD	253.54±102.41	246.9±101.41	257.5±103.1	0.416*
Total Cholesterol	Mean±SD	177.73±39.79	178.52±43.95	177.24±37.14	0.792*
HDL (mmol/L)	Mean±SD	48.31±12.95	50.32±13.44	47.08±12.53	**0.039***
LDL (mmol/L)	Mean±SD	106.62±33.81	106.78±36.84	106.52±31.93	0.948*
Triglyceride	Mean±SD	124.11±103.63	117.17±89.65	128.34±111.34	**0.025****

*Independent t test, **Mann Whitney U test +Chi Square test. "BMI, body mass index; FBS, fasting blood sugar; HOMA-IR, homeostatic model-assessment-insulin resistance; AMH, Anti-mullerian hormone; FSH, follicle stimulating hormone; LH, Luteinizing Hormone; E2, estradiol; DHEAS, Dehydroepiandrosterone; HDL, High-density lipoprotein; LDL, Low-density lipoprotein.

In order to compare the LH value of ovulatory and anovulatory phenotypes, an independent-sample t-test was conducted. There was a statistically significant association between ovulatory and anovulatory phenotypes in women with PCOS in terms of age ($p<0.05$). It showed that the LH of the ovulatory group (M=9.93, SD=5.62) was lower than the LH of the anovulatory group (M=11.24, SD=4.78).

There was a statistically significant association between ovulatory and anovulatory phenotypes in women with PCOS in terms of HDL ($p<0.05$). It showed that HDL of the ovulatory group (M=50.32, SD=13.44) was higher than LH of the anovulatory group (M=47.08, SD=12.53).

There was not a statistically significant association between ovulatory and anovulatory phenotypes in women with PCOS in terms of AMH, FSH, E2, TSH, Testosterone, free testosterone, DHEAS, total cholesterol, and LDL ($p>0.05$).

In order to compare the triglyceride value of ovulatory and anovulatory phenotypes, the Whitney U test was conducted. There was a statistically significant association between ovulatory and anovulatory phenotypes in women with PCOS in terms of triglyceride (p-value<0.05). It showed that the triglyceride of the ovulatory group (Median=94.5) was lower than the triglyceride of the anovulatory group (Median=103.5).

DISCUSSION

The present study expanded the previous findings, and based on the comparison findings of mentioned parameters between the two subgroups, no significant relationship was observed in most of the parameters. In our study, BMI, waist/hip ratio, FBS, HOMA-IR, AMH, FSH, E2, TSH, testosteron, free Testosteron, DHEAS, total cholesterol, and LDL were similar between ovulatory and anovulatory phenotypes. This study showed statistically significant difference between the two phenotypes in age, insulin, LH, HDL, triglyceride parameters. Age of women suffering from PCOSwas relatively low in anovulatory compared to the ovulatory group. The insulin valuewas relatively high in anovulatory in comparison to ovulatory group. The LH and triglyceride values were relatively low in ovulatory in comparison to anovulatory group. The HDL value was relatively high in ovulatory contrasted to anovulatory group.

Clinical, biochemical parameters and metabolic distinctions between PCOS subgroups have been expressed in various research. Panidis et al.[17] compared insulin resistance (IR) and endocrine characteristics of the different phenotypes (severe PCOS, anovulation and hyperandrogenemia, ovulatory PCOS, and mild PCOS). Severe PCOS is associated with more IR. IR also describes the anovulation and hyperandrogenemia with obesity. In contrast, ovulatory PCOS is not associated with IR. The results of the present study are compatible with this study, and no significant relationship was observed between the two phenotypes in terms of IR.

We did not find a significant difference between HOMA-IR and PCOS phenotypes (ovulatory and anovulatory groups), which is consistent with some

previous studies.[18,19] Gupta et al.[19] evaluated the BMI, AMH and IR in three PCOS phenotypes and reported that no correlation of IR among the different phenotype groups. Hosseinpanah et al.[18] in a retrospective study with 915 women, compared metabolic features, HOMA-IR and fasting insulin among four PCOS phenotypes. They reported no significant difference between PCOS phenotypes and study parameters. Contrary results were presented by Al-Jefout et al.[20] who reported that IR and obesity in severe PCOS phenotype were significantly higher than other three main PCOS phenotypes. Shirazi et al.[21] showed a higher risk of IR in the phenotype oligomenorrhea/amenorrhea (O), hyperandrogenism (H), and polycystic ovary morphology (P). These result has been repeated in other studies.[22,23] This disagreement may result from various analysis methodologies, PCOS type standards, determining standards for IR, and cut-off values for HOMA-IR.

We did not find a significant difference between clinical and biochemical parameters (expect insulin, LH, HDL and triglyceride) and PCOS phenotypes (ovulatory and anovulatory groups), which is consistent with a previous study. Mansour et al.[24] in a cross-sectional secondary analysis with 125 Iranian women, compared twenty-four clinical and biochemical parameters among PCOS phenotypes. They reported no significant difference in all parameters except fasting blood sugar.Guastella et al.[25] assessed the endocrine and clinical distinctions between four PCOS phenotypes. They showed nosignificant difference between PCOS two most common phenotypes (type I classic PCOS and type II classic PCOS) in terms of endocrine and clinical parameters. Burgers et al.[15] in a retrospective cohort study with 1750 women, compared endocrine, ultrasound, and clinical parameters between anovulatory and oligoovulatory women with PCOS. They reported that women suffering from oligoovulatory phenotypes show a milder ovarian dysfunction phenotype than anovulatory PCOS patients.

Limitations of the study

This study has some limitations. Characterization of features associated with PCOS phenotypes has varied between studies. This situation caused difficulties in comparing our study with previous studies. To our knowledge, this is the first study to comparatively examine clinical and biochemical parameters in a cohort of Turkish women and specifically focus on identifying differences between anovulatory and ovulatory individuals.

CONCLUSION

There is no significant difference in PCOS's ovulatory and anovulatory phenotypes in essential parameters such as insulin resistance and BMI. More extensive and complete studies are needed to investigate the differences in phenotypes regarding metabolic, clinical, and biochemical parameters.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstinye University Ethics Committee (Date: 22/09/2023, Decision No: 2023/09).

Informed Consent: Because the study was designed retrospectively, no writtenin formed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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I was originally born in 1975 in İstanbul. After graduating from Uludağ University Faculty of Medicine, I successfully completed my obstetrics and gynecology specialization training in İstanbul SSK Okmeydanı Hospital in 2004. I continued mycareer in private hospitals providing tertiary health care services, and during this time. I had the opportunity to work and learn with experts who are appreciated in their field. I have attended trainings on minimally invasive surgery abroad and in the country. I have attended more than 50 national and international congresses. Recently, I have published articles of which I am the author or contributed, and there are 4 book chapters of which 2 of them are in the process of publication. Finally, I have been working actively at Liv Hospital VadİstanbulHospital in affiliation with the University of İstinye with my experience of more than 15 years, while continuing my academic studies. My command in English is very good. I am married and have one daughter.

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A study on the factors affecting polycystic ovary syndrome in young women

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ABSTRACT

Aims: The aim of this study was to define the incidence of polycystic ovary syndrome (PCOS) in young women and the affecting characteristics. In this study, environmental factors and demographic characteristics of women with PCOS were compared with the control group, which included healthy young women.

Methods: This is a retrospective study with control in young women aged 18-25, suffering from PCOS and healthy women, referred to our clinic between September 2018- August 2020. Women's socio-demographic characteristics such as age, weight, height, economic status, employment status, education status, smoking and alcohol abuse, chronic disease, exercise status, family history of cancer, and menstrual irregularity of participants were compared.

Results: Results did not show a statistically significant association between case and control regarding age, economic status, education status, family history of cancer, smoking and alcohol abuse ($p>0.05$). There was a statistically significant difference between groups regarding menstrual irregularity, chronic disease, body mass index (BMI), exercise and working status ($p<0.05$). Healthy women exercise more, and a higher percentage of them are employed. Chronic diseases were more common in women with PCOS. Women with PCOS were fatter and had more menstrual irregularities problems.

Conclusion: BMI, working status, exercise status, menstrual irregularity, and chronic disease status helped diagnose PCOS in young women.

Keywords: Polycystic ovary syndrome, PCOS, young women, BMI, menstrual irregularity.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common syndrome and one of the causes of infertility in women of reproductive age, which has profound effects on the lives of young women.[1,2] Its most important clinical symptoms are menstrual disorders, skin diseases caused by the increase of endogenous hormones such as acne, hirsutism, and hair loss, brown areas on the neck and arms due to insulin resistance, and problems related to pregnancy such as irregular ovulation, infertility, and repeated abortion.[3,4] The effects of this syndrome on the pregnancy process in young women have revealed the importance of research on this disease.

In the examination of serum tests of women with PCOS, it has been found that they have lower levels of follicle stimulating hormone (FSH), Sex hormone-binding globulin (SHGB), and High-density lipoprotein (HDL) hormones. Also, Luteinizing Hormone (LH), testosterone, insulin, cholesterol, and triglyceride hormone levels are higher in these women than in healthy women.[5,6] These factors cause obesity, insulin resistance, and high blood pressure, which in the long run increases the risk of type 2 diabetes and cardiovascular diseases.[7] PCOS, which affects women in many ways, also causes a decline in quality of life.[8,9] PCOS is a significant health issue affecting all periods of women's lives, especially young adulthood.[10]

Over the past two decades, many studies have been conducted to find the causes of PCOS. Genetic factors are influential factors in this syndrome, and the etiology of this syndrome proves that it is hereditary.[11] More than 70 effective candidate genes in this syndrome have been evaluated in previous studies; however, due to genetic and phenotypic heterogeneity, the results of these studies remained inconclusive.[12] Limited studies have been conducted on environmental and demographic factors' role in this syndrome.

This study compared the demographic characteristics and lifestyle of young women with PCOS with healthy women. This study aimed to identify the different parameters in

women with this syndrome. As the newest and most advanced treatment method, person-centered medicine emphasizes individual characteristics. In this method, treatment and lifestyle suitable for each person are provided based on the characteristics of each person. The main goal of this study is to identify environmental factors that are effective in this disease and provide effective treatment methods based on person-centered medicine. This study was conducted to determine the factors affecting PCOS in young women.

METHODS

The study was carried out with the permission of Beykoz University Ethics Committee (Date:12.01.2021, Decision no:1). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki and documented declared permission was received from all women.

This is a retrospective study with women aged 18-25, referred to the Beykoz University Hospital between September 2018-August 2020. This study divided women with PCOS into two groups: Women with PCOS as a case group (n=100) and healthy women (n=150). This study gathered data with the patient inquiry form. In the patient inquiry form, women's socio-demographic characteristics such as age, weight, height, economic status, employment status, education status, smoking and alcohol abuse, chronic disease, exercise status, family history of cancer, and menstrual irregularity were questioned.

Women participating in this study were classified into three groups based on the body mass index (BMI) value. Underweight fora BMI less than 18.5 kg/m^2, normal weight fora BMI greater than or equal to 18.5 to 24.9 kg/m^2 and overweight fora BMI greater than or equal to 25. The economic status of the family was determined based on the family income. It was classified as a low-income family if it was less than 300 dollars. If it was between 300-800 dollars, it was classified as a middle-class family, and more than that was classified as a wealthy family. It was considered a regular exercise activity if a person exercises more than three times during the week and each time for more than 1.5 hours. For alcohol abuse, study participants were classified as women who consumed more than seven drinks per month. Study participants were classified as smokers if they smoked more than five weekly cigarettes.

Statistical Analysis

The Pearson chi-square test was used to compare qualitative data. After the normality test of age and BMI data by using the Shapiro-wilk test, Independent Samples t-test was used to compare between two groups. Mean (M) and standard deviation (SD) were used for descriptive characteristics for numerical values. SPSS v22was used for statistical analyses. A value of $p<0.05$ was accepted as statistically significant.

To calculate the sample size with the G-Power 3.2 program, difference between two independent proportions was measured based on the Pearson's Chi-Square Test of Association with the power of 80%, effect size of 50%, and 0.25 type 1 error for at least 228 patients.[13]

RESULTS

A total of 250 young women participated in this study. Table 1 shows the comparison of women with suffering from PCOS and healthy group in study parameters.

Table 1. The significant relationship between women with suffering from PCOS and healthy groups

Study parameters		Total (n=250) n (%)	Case (n=100) n (%)	Healthy women (n=150) n (%)	*p*-value
Age		22.29±1.91	21.95±0.96	22.63±3.14	0.129*
BMI		24.86±0.98	26.18±1.05	23.98±1.07	**0.02***
Working status	Employed	85 (34)	25 (25)	60 (40)	**0.04****
	Unemployed	165 (66)	75 (75)	90 (60)	
Economic status	Wealthy	61 (24.4)	23 (23)	37 (25.3)	0.194**
	Middle	160 (64)	66 (66)	94 (62.6)	
	Low-income	29 (11.6)	11 (11)	18 (12)	
Education status	High school	145 (58)	60 (60)	85 (56.6)	0.812**
	University	105 (42)	40 (40)	65 (43.4)	
Smoker	Yes	30 (12)	13 (13)	17 (11.3)	0.108**
	No	220 (88)	87 (87)	133 (88.7)	
Alcohol abuse	Yes	70 (28)	25 (25)	45 (30)	0.091**
	No	180 (72)	75 (75)	105 (70)	
Chronic disease	Yes	28 (11.2)	20 (20)	8 (5.3)	**<0.001****
	No	222 (88.8)	80 (80)	142 (94.7)	
BMI groups	Underweight	50 (20)	19 (19)	31 (20.6)	**<0.001****
	Normal	136 (54.4)	31 (31)	105 (70)	
	Overweight	64 (25.6)	50 (50)	14 (9.4)	
Exercise status	Yes	44 (17.6)	11 (11)	33 (22)	**0.038****
	No	206 (82.4)	89 (89)	117 (78)	
Family history of cancer	Yes	15 (6)	5 (5)	10 (6.7)	0.109**
	No	235 (94)	95 (95)	140 (93.3)	
Menstrual irregularity	Yes	90 (36)	51 (51)	39 (26)	**0.014****
	No	160 (64)	49 (49)	111 (74)	

*A Independent Samples t-test, **A Chi-square test, BMI: body mass index.

Table 1 shows the comparison of women with suffering from PCOS and healthy group on the study parameters. As stated in Table 1, an independent Samples t-test did not find a statistically significant association between case and control regarding age ($p>0.05$). There was a significant association between two groups in terms of BMI ($p<0.05$). It indicated that BMI of case group (M=26.18, SD=1.05) were higher than BMI of healthy women (M=23.98, SD=1.07). There [was or was not] a significant relationship between the two variables.

The relationship between the working status and suffering from PCOS was assessed using a Pearson's Chi-Square Test of Association. There was a significant relationship between the two variables ($p<0.05$). As can be seen from the table 1, there was not a statistically significant association between healthy women and women with PCOS regarding economic status, education status, family history of cancer, smoking and alcohol abuse ($p>0.05$).

There was a significant relationship between the chronic disease status and suffering from PCOS ($p< 0.05$). There was a significant relationship between BMI groups and suffering from PCOS ($p<0.05$). There was a significant relationship between the exercise status and suffering from PCOS ($p< 0.05$). The Pearson's Chi-Square Test of Association found a significant relationship between the menstrual irregularity and suffering from PCOS ($p< 0.05$).

Figure shows the parameters that significantly differ between the two groups. The numbers specified in this figure are in percentage form.

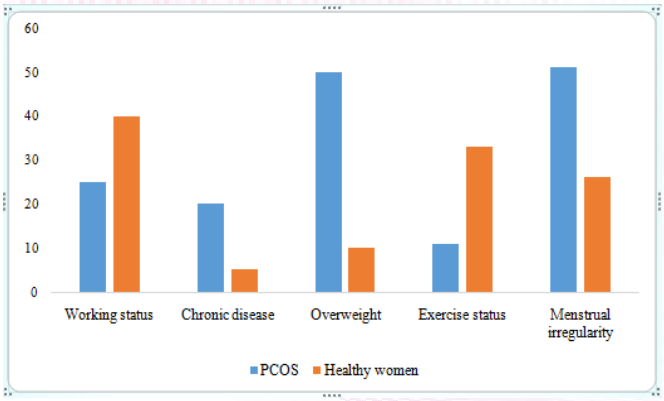

Figure. The parameters have a significant difference between the two groups

DISCUSSION

Based on the study's findings, a significant difference was reported between the two groups of cases and healthy women in terms of BMI, working status, chronic disease, exercise status, and menstrual irregularity parameters. In this study, the percentage of employed women in the case group was lower than healthy women (25% vs. 40%). Women suffering from chronic disease had a higher percentage in the case group (20% vs. 8%). The percentage of athlete women in the case group was three times lower than healthy women (11% vs. 33%). The prevalence of menstrual irregularity in women with PCOS is twice as high as in healthy women (51% vs. 26%). In this study, consistent with previous studies, obesity is more common in women with PCOS (50% vs. 9.4%).

Obesity, overweight, and visceral fat accumulation are common in women with PCOS. More than 50% of these women are obese. In the present study, obesity and overweight in case group women were significantly more than healthy women. These results are consistent with previous studies.[14,15] Whether PCOS is the cause of obesity or obesity causes this disease is one of the challenging issues, and no exact answer has been provided by the researchers yet.[16]

This study showed statistically significant difference between two groups in terms of chronic disease. The prevalence of chronic diseases in healthy women is lower than in women with suffering from PCOS. Based on research, PCOS is extremely correlated with numerous chronic diseases, such as glucose intolerance, high blood pressure, hypercholesterolemia, diabetes mellitus type 2, and hepatic steatosis.[17] Increased insulin resistance in women with PCOS causes increased blood lipid levels. This position raises women's risk of cardiovascular disease as a chronic disease.[18]

Wang et al.[19] in a prospective study with 1127 women aged 19-32, showed no association between smoking and PCOS. They also did not report a significant relationship between alcohol abuse and PCOS. Previous studies showed that smoking can also cause irregularities in the menstrual cycle due to the imbalance in estrogen and FSH levels.[20,21] However, there was no significant difference between the two groups of smoking prevalence in this study because the participants were 18-25 years old, and they were not exposed to the impact of long-term smoking and alcohol abuse. Due to the damaging effects of alcohol and smoking in the long term, women with PCOS are advised to lead a healthy lifestyle and avoid smoking and alcohol.

Regular exercise's effect on lowering PCOS disease symptoms is evident. Harrison et al.[22] reported that regular sports intervention (either in resistance or aerobic sports) improves menstrual cycles and increases the possibility of reproduction. Butt et al.[23] in a systematic review, showed that physical activity reduces infertility, as well as psychological and social stress among women. However, it is impossible to comment on regular exercise's role in contracting this disease. In this study, a higher percentage of healthy women exercised regularly than patients.

The prevalence of menstrual irregularity in women with PCOS was predictable. Changing lifestyle through changes in diet and regular exercise programs is one of the low-cost and effective methods to improve the symptoms of patients with PCOS. Many researchers have emphasized it for decades.[23-25]

CONCLUSION

Finding the cause of the disease and the factors that aggravate the symptoms of PCOS is a way to provide treatments and solutions for this disease in person-centered medicine. This study found that the index of exercise and employment status, BMI, and chronic disease status of women affect the diagnosis of PCOS. Therefore, it is very important to determine the nutritional habits of women and increase physical and balanced activities to have a normal BMI. It is recommended that these patients become more aware of the cause of the disease, diagnostic criteria, symptoms, effective

factors, and long-term and short-term health problems of PCOS in order to manage this disease with low-cost solutions such as diet and exercise.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Beykoz University Ethics Committee (Date:12.01.2021, Decision No:1).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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Investigating the association between hyperprolactinemia and thyroid autoimmunity in women

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ABSTRACT

Aims: Hyperprolactinemia (HPRL), a condition characterized by elevated levels of prolactin (PRL) hormone, is considered to be related to various autoimmune diseases, such as thyroid autoimmunity (TAI). The association between HPRL and TAI still evokes controversy. Our study intends to examine the possible relationship between HPRL and TAI in young women.

Methods: This retrospective study was done between January 2018 and December 2022, including 90 women with HPRL and 90 control subjects of similar age and gender. A retrospective examination was conducted on the medical records of 90 patients with HPRL to gather relevant data. Information regarding related parameters was analyzed and compared to the control group data.

Results: Our results found that thyroid stimulating hormone (TSH) levels were notably elevated in patients with HPRL compared to healthy women (2.24 vs. 1.86). Also, a statistically significant association between the case and control regarding serum free triiodothyronine (fT3) ($p<0.05$). No statistically significant difference was found between the case and control regarding serum free thyroxin (fT4) ($p>0.05$). Patients with HPRL demonstrated considerably higher anti thyroperoxidase antibody (anti-TPO) levels (46.08 vs. 43.95). Significantly elevated antithyroglobulin antibody (anti-Tg) levels were observed in patients with HPRL (1.07 vs. 0.84).

Conclusion: The study suggests a potential link between HPRL and TAI. Further research is needed to explore this relationship and its implications for patient care.

Keywords: Hyperprolactinemia, HPRL, thyroid autoimmunity, autoimmune diseases

INTRODUCTION

Hyperprolactinemia (HPRL), a condition characterized by elevated levels of prolactin (PRL) hormone, has been associated with various autoimmune diseases, such as thyroid autoimmunity (TAI).[1] TAI, on the other hand, is the most frequent autoimmune disease among reproductive-aged women and is associated with conditions such as Hashimoto's thyroiditis and Graves' disease. Autoimmune thyroid diseases affect a significant portion of the population and it can be also associated with low β-HCG levels in pregnant women and iron deficiency anemia.[2,3] Research has shown that 20% of autoimmune thyroid disease patients have HPRL, with twice the occurrence in those with hypothyroidism.[4]

Moreover, studies have reported that thyroid autoantibodies are seen in 25% of patients with HPRL than in 22% of controls.[5] Although HPRL and TAI have been widely studied, the relationship between these conditions remains unclear and warrants further investigation.

Some studies have found no increased prevalence of TAI among individuals diagnosed with HPRL in comparison to healthy controls.[6] However, other research has shown that patients with HPRL have a notable increase in the volume of thyroid, the prevalence of thyroid nodules, and autoimmunity among the population studied.[7] Additionally, another study shows that female patients with prolactinomas are more likely to have autoimmune thyroid diseases than the general population.[8] The prevalence of clinical symptoms, such as dry skin and cold weather intolerance, is not reported in patients with HPRL, with a significant difference compared to those without it.[9]

The main contribution of this study is to investigate the possible relationship between HPRL and TAI in young Turkish women. The association between autoimmune thyroid disease activity and PRL levels remains controversial. Our study aims to examine the possible relationship between HPRL and TAI. By identifying any potential association between HPRL and TAI, our study may add to a more in-depth understanding of the pathogenesis of these conditions and inform the development of new treatment options.

METHODS

This retrospective study was conducted on patients between January 2018 and December 2022. The study was approved by Bezmialem Vakıf University Hospital Ethics Committee (Date: 03/04/2023, Decision No: 2023/74). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

By concentrating on patients with autoimmune features, this study intends to investigate the link between HPRL and primary thyroid diseases. The study's sample size was 90 women with HPRL and 90 age and gender-matched control subjects. A retrospective examination of the medical records of the study subjects was conducted to gather relevant data. Information regarding thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), circulating free thyroxine (fT4), anti thyroperoxidase (anti-TPO), and antithyroglobulin (anti-Tg) was analyzed.

The study did not include women using medications affecting thyroid and prolactin levels. Women who had chronic diseases and were not between 25-40 years old were also excluded from the study.

In order to assess TAI, the study compared the frequency of elevated anti-Tg and/or anti-TPO levels among patients and control subjects. The link between serum PRL levels and thyroid autoantibodies was also examined. Finally, the study analyzed the relationship between HPRL and TAI. Following this methodological approach, the study aimed to provide valuable insights into the potential connection between thyroid disorders and HPRL, emphasizing patients with autoimmune traits.

Statistical Analysis

The study used medians (range) to report the data results. To compare the data between groups, the Mann-Whitney U test was employed, which is appropriate for non-normal distributions. SPSS software (version 18.0, SSPS Inc., Chicago, IL, USA) was used to perform the statistical analysis. The threshold for statistical significance was set at a p-value of less than 0.05.

RESULTS

This study included one hundred eighty age-matched (31.77±3.94) and body mass index (BMI) matched (24.98±0.99) women. Table 1 shows descriptive statistics of the parameters of the study in women.

Table 1. Statistical description of study parameters in participants

Study parameters	median (range) mean ± SD
Age	33 (24-39) 31.77 ± 3.94
BMI	24 (22-28) 24.98±0.99
TSH	2 (1.48-2.96) 2.12 ± 0.42
fT3	3 (2.74-1.47) 2.98 ± 0.18
fT4	1 (0.88-1.52) 1.14 ± 0.21
Anti-TPO	10 (3-66) 28.87 ± 19.74
Anti-Tg	2 (1.45-6) 19.69 ± 18.15

BMI:Body mass index; TSH: thyroid stimulating hormone; fT3: free triiodothyronin ; fT4: free thyroxine; anti-TPO: anti thyroperoxidase antibody; anti-Tg: antithyroglobulin antibody.

Two groups were formed for the study: Group 1, which had 90 patients (mean age: 31.44 ± 2.19), and Group 2, comprising 90 control subjects (mean age: 31.98 ± 2.89). The mean BMI of group 1 was (25.06 ± 1.01) and group 2 was (24.77 ± 0.96). There were no notable differences in age between the two groups ($p > 0.05$).

Table 2. Comparison of case and control groups

Study parameters	Case (patients with hyperprolactinemia)	Control (n=90) M±SD	p-value
(n=90) M±SD	Control	31.98±2.89	0.879
(n=90) M±SD	p-value	24.77±0.96	0.749
Age	31.44±2.19	31.98±2.89	0.879
BMI	25.06±1.01	24.77±0.96	0.749
TSH	2.24±1.36	1.86±1.19	<0.001
fT3	3.35±1.59	3.01±1.3	0.028
fT4	1.28±0.68	1.18±0.61	0.09
Anti-TPO	46.08±5.86	43.95±2.27	0.034
Anti-Tg	1.07±0.28	0.84±0.51	<0.001

As stated in Table 2, a statistically significant association was observed between the case and control regarding serum TSH ($p<0.05$). Patients with HPRL had significantly higher TSH levels than healthy controls (2.24 vs. 1.86).

As stated in the table above, a statistically significant association was observed between the case and control regarding fT3 ($p<0.05$). The fT3 levels were significantly higher in patients with HPRL (3.35 vs. 3.01). The case and control groups did not demonstrate a statistically significant difference regarding fT4 ($p>0.05$).

As stated in the table above, a Mann-Whitney U test found a statistically significant association between case and control regarding Anti-TPO ($p<0.05$). Anti-TPO levels were significantly higher in patients with HPRL (46.08 vs. 43.95).

Table 2 showed a statistically significant association between case and control regarding Anti-Tg ($p<0.05$). Anti-Tg levels were significantly higher in patients with HPRL (1.07 vs. 0.84). Figure shows the study's findings and parameters' differences in the groups.

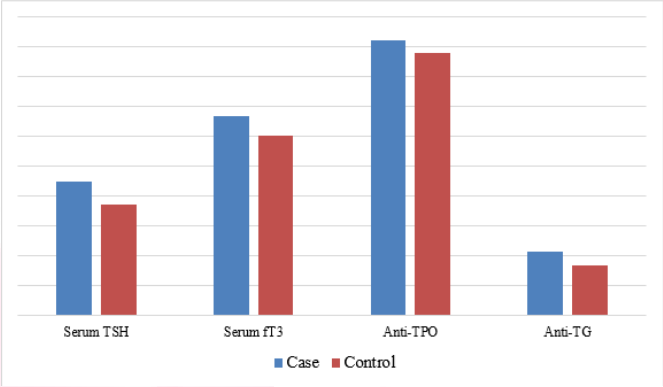

Figure. Study's findings and parameters' differences in the groups

DISCUSSION

This study investigated the possible relationship between HPRL and TAI. It is important to study the relationship between TAI and HPRL because high prolactin may have caused hypothyroidism or vice versa. Reduction of thyroid in the body can cause prolactin to increase or decrease. As a result, if a woman has hypothyroidism and her prolactin is high, prolactin treatment can return the thyroid to normal. Therefore, identifying the influential factors can provide more effective treatments.

The findings indicated that compared to healthy controls, TSH, fT3, anti-TPO, and anti-Tg levels were significantly elevated in patients with HPRL. The current findings are in agreement with previous studies that have reported a relationship between HPRL and thyroid dysfunction. For instance, a study by Sahu et al.[10] found significantly increased serum PRL levels in patients with both clinical and subclinical hypothyroidism, and HPRL was observed in 22.9% of patients with subclinical hypothyroidism and 8.3% of clinical hypothyroidism. In another study conducted by Kumari et al.[11] a positive association between PRL levels and serum TSH was observed in infertile women. The study identified HPRL in 7% of the control group and 57% of infertile women.

Other studies have also reported the association between HPRL and TAI. A study by Unluturk et al.[11] found that among patients exhibiting autoantibody positivity, thyroid function test irregularities were more prevalent in HPRL patients (60%) compared to controls (9.1%). Similarly, Sahu et al.[9] conducted a study that found a correlation between PRL and TSH levels in patients with clinical and subclinical hypothyroidism.

While several studies have reported a relationship between HPRL and TAI, some studies have not found a significant association between the two conditions. For example, in a study by Onal et al.[12] untreated prolactinoma patients did not exhibit an increased incidence of TAI when compared to healthy individuals. Similarly, a study by Venables et al.[13] showed that TAI does not influence the outcomes of the pregnancy in either euthyroid women or women with subclinical hypothyroidism.

One study examined a total of 100 patients diagnosed with HPRL and found that 25% of them had positive anti-TPO and anti-Tg, which are markers of TAI. Among these patients, the frequency of thyroid function test abnormalities was higher than in controls.[11] Another study found that patients with HPRL had a higher prevalence of TAI than controls, but the difference was not statistically significant.[14]

Other research has examined the impact of iodine supplementation on TAI and found that while iodine prophylaxis may have some risks for TAI, in a population with a stable median iodine concentration of up to 300 µg/L, the benefits are significantly greater than the risks.[15] The pathogenesis of TAI is complex and involves genetic and environmental factors. Environmental factors such as exposure to pollutants and endocrine disruptors have been implicated in developing autoimmune thyroid disease.[16]

The inconsistent results across studies could be attributed to several factors, such as differences in study populations, sample sizes, and methodologies. Additionally, the relationship between HPRL and TAI might be influenced by various factors that could act as confounders, such as gender, age, and comorbid autoimmune diseases.[17] It is also possible that the association between HPRL and TAI is not direct but mediated by other factors, such as hormonal imbalances or immune system dysregulation.[18]

The underlying mechanisms linking HPRL and TAI are not yet fully understood. However, it has been suggested that PRL levels may have immunomodulatory effects, influencing the immune response and contributing to the development of autoimmune thyroid diseases.[19] Additionally, thyroid-releasing hormone (TRH) stimulates the secretion of both PRL and TSH, which may lead to elevated PRL levels in patients with thyroid dysfunction.[20]

The relationship between HPRL and TAI is not fully understood, but several potential mechanisms have been proposed. One possible mechanism is that HPRL may trigger an autoimmune response that leads to TAI. PRL levels has been shown to have an immunostimulatory effect, mainly through the inhibition of autoreactive B lymphocytes' negative selection.[21] This effect may lead to the production of autoantibodies that attack the thyroid gland, causing TAI.[22] Another possible mechanism is that there may be a genetic link between HPRL and TAI. Chromosome 6's short arm contains the PRL gene, which is also associated with several autoimmune diseases, including autoimmune thyroiditis.[23] A third possible mechanism is that HPRL may affect the levels of thyroid hormones in the body, leading to TAI. PRL levels has been shown to inhibit the secretion of TSH, resulting in an effect on the synthesis of thyroid hormones by the thyroid gland.[24] Finally, it has been suggested that treating HPRL may lead to the development of TAI. Some medications used to treat HPRL, such as dopamine agonists, have been associated with developing autoimmune thyroiditis.[25]

In conclusion, the association between HPRL and TAI is complicated and not fully understood. Several potential mechanisms have been proposed, including autoimmune, genetic, hormonal, and treatment-related mechanisms. Further research is needed to fully understand the relationship between these two conditions.

Limitations of the Study

As with any study, our study also had some limitations. The first limitation is the cross-sectional design of the study, meaning it only provides a snapshot of the relationship between HPRL and TAI at a single point in time. This limits the ability to conclude causality or the direction of the relationship. The sample size is relatively small, with only 90 women with HPRL and 90 control subjects. Therefore, the findings may not be generalizable to other populations. This study did not include men because of the limited work done on Turkish women. The focus of the study was on women. Finally, the research was based on a retrospective examination of medical records to gather data, which may introduce bias or errors in the data collection. Despite these limitations, the study provides valuable insights into the potential association between HPRL and TAI, and further research is necessary to verify and expand upon our findings.

CONCLUSION

The current study explored the potential association between HPRL and TAI. Patients with HPRL exhibited significantly elevated levels of TSH, fT3, anti-TPO, and anti-Tg compared to healthy controls, according to the results. Previous research has reported a relationship between thyroid dysfunction and HPRL, which is consistent with the current findings. This study implies that patients presenting with HPRL or TAI should be evaluated for both conditions, as they may be closely related. More research is needed to elucidate the mechanisms and explore potential therapeutic approaches for patients with HPRL and TAI. Overall, this research contributes to the growing body of research on the correlations between HPRL and TAI, highlighting the importance of considering both conditions in clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bezmialem Vakıf University Hospital Ethics Committee (Date: 03/04/2023, Decision no: 2023/74).

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Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Review

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Eating disorders associated with polycystic ovary syndrome (PCOS), a literature review

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a common enigmatic, heterogenous endocrine disorder with multisystem consequences affecting women at reproductive age. Most associated dysfunctions in PCOS patients include ovarian dysmorphology, hormonal imbalances, metabolic disturbances, and neuropsychological impairments. Emerging studies have shown a relationship between women with PCOS and eating disorders (ED). ED is described as a psychological disorder characterized by extreme and constant disruptions in eating behaviors that can negatively impact one's mental health and status. Types of EDs include binge eating disorder (BED), bulimia nervosa (BN), anorexia nervosa (AN), other specified feeding or eating disorders (OSFED), and unspecified feeding and eating disorders (UFED). Understanding the clinical relevance of these associations and adding correct assessments of ED as a key determinant of eating behavior may contribute to the successful treatment of women with PCOS. Thus, this review aims to outline a more profound connection between the involvement of multiple eating disorders and related disordered eating in women with PCOS; it also establishes a wider overview regarding the prevalence of comorbidities in eating disorders. Furthermore, the majority of researchers advised that screening for eating disorders, PCOS phenotyping, and neuroimaging modalities can be utilized to provide a better health outcome in PCOS patients. PubMed and Web of Science databases were searched for reviews on this issue.

Keywords: Polycystic ovary syndrome, PCOS, eating disorders, bulimia nervosa, anorexia nervosa

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogenous multisystem disorder mostly affecting women of reproductivewith an increasing prevalence recently estimated to be 10%-13%.[1-3] PCOS is characterized by a diversity of endocrine-metabolic, psychological, and reproductive manifestations, examples of each including hyperandrogenism-hyperinsulinism, poor self-esteem, and polycystic ovarianmorphological abnormalitiesrespectively. In addition to these factors, clinical features like hirsutism, acne appearance, elevated body mass index (BMI), and obesity have contributed to adverse eating psychological disorders that have become progressively apparent in patients with PCOS.[4]

Eating disorders(ED) are a broad spectrum of complex psychological disorders with a strong female predominance that is characterized by abnormal eating behaviors that may or may not be accompanied by compensatory behaviors.[4,5] Various types of eating disorders include bulimia nervosa (BN), anorexia nervosa (AN), binge eating disorder (BED),[5-7] other specified feeding or eating disorders (OSFED),[7,8] and unspecified feeding and eating disorder (UFED).[8,9] BED is a condition marked by overeating without subsequent purging.[9] AN is characterized by severely limiting energy intake, which leads to low body weight, along with strong anxiety about gaining weight and distorted perceptions of body shape.[10,11] BN occurs recurrently by having binge eating episodes with loss of control when these episodes happen andis accompanied by improper coping mechanisms.[7,11,12] Globally, the estimated prevalence of any ED is around 1%.[5] These disorders are most likely the result of complex interactions between biological, social, cultural, as well as individual factors.[13,14] Food restriction, binge eating, purging, the use of laxatives, diet medication, and excessive exercise are all behaviors that fall under the category of eating disorders.[4] The impact of an ED and its symptoms on all aspects of a person's life has been widely documented, with studies finding decreased interpersonal functioning as well as mental and physical concerns that are associated with higher morbidity and healthcare expenses.[15-18] As a result,

eating disorders exacerbate obesity and metabolic syndrome, creating a perpetual vicious cycle[19].BED is the most common ED associated with women suffering from PCOS.[5] Overall, this present review adopts an integrative theoretical conception that aspires to shed light on the co-existence of different types of ED (BED, BN, EED, NES, AN) and (PCOS). PubMed and Web of Science databases were searched for reviews on this issue.

PATHOPHYSIOLOGY

PCOS

PCOS is characterized by irregular ovulation, increased androgens levels, abnormal GnRH pulsation, and insulin insensitivity.[20] PCOS is characterized by a reciprocal relationship between hyperandrogenism and insulin resistance, with higher levels of insulin leading to the development of hyperandrogenism and vice versa (Figure 1). Furthermore, dysfunction in the hypothalamus-pituitary-adrenal (HPA) axis results in elevated levels of androgens and insulin resistance. These factors all contribute to the development of PCOS.[20]

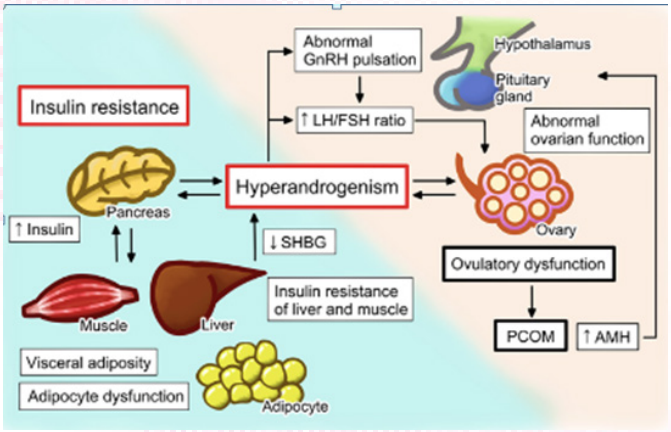

Figure 1. Effects of Insulin resistance and hyper and rogenism[20]

In addition to these associated contributors, it has been observed that there is a strong familial pattern in patients with this condition.[21] PCOS mothers show high androgenic hormone levels in the uterus resulting from raised androgen levels and impaired placental functioning. This in turn leads to the fetus' ovaries secreting increased levels of androgens in response to the intrauterine atmosphere of mothers with PCOS.[21] Research has indicated that prenatal androgen exposure can upset the intestinal microbial balance, potentially leading to PCOS later on.[20] Further, studies have suggested that PCOS and elevated concentrations of androgen in the uterus may increase the odds of their offspring suffering from neuropsychiatric disorders, for example, autism, ADHD, and Tourette Syndrome.[21]

Studies with pregnant mice showed that supplying the uterus with Antimüllerian hormone (AMH) caused offspring to exhibit signs of PCOS, such as hyperandrogenism and enlarged LH pulses, leading to reduced ovulation in female offspring (Figure 2). Those with anovulatory PCOS have more AMH than those with ovulatory PCOS.

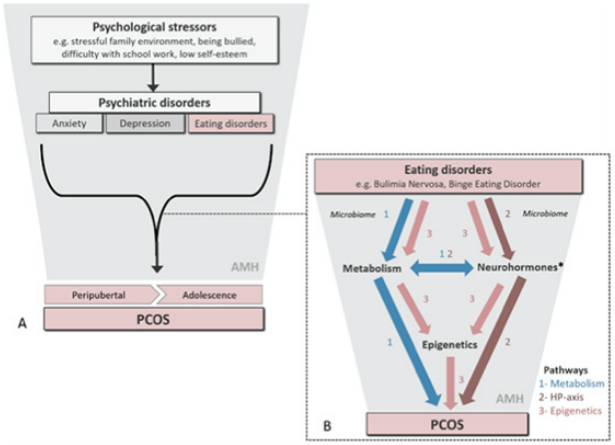

Figure 2. Effects of psychological stressors on developing of eating disorders in PCOS patients[14]

Psychosomatic Aspects in PCOS

Manifestations of psychological issues among patients with PCOS may be attributed to the connection between the mind and body, which can occur through three main pathways. These includedysregulation of neurotransmitters which is the main attribute of PCOS, instability in the neuroendocrine axis, and disruptions in the brain-gut axis.[4]

Neurotransmitter dysregulation: Neurotransmitters appear to be involved in sustaining mental equilibrium and some psychiatric issues. Major depression is attributed to an impairment of the monoamine systems, notably serotonin (5-HT), noradrenaline (NE), and dopamine (DA). Other than depression, imbalances in glutamate, gamma aminobutyric acid (GABA), and acetylcholine levels can lead to anxiety-related disorders. It also appears that those with PCOS and depression may have altered morphine levels. Generally, neurotransmitter imbalances can lead to reduced self-worth, anxiety, emotional fluctuations, irritability, and depression. Low concentrations of these mediators can cause irregular LH release in PCOS patients, potentially resulting in a neuroendocrine disorder.[4]

Neuroendocrine axis instability: The CNS's androgen receptors, insulin receptors, GABA transmissions, and internal opioid signaling likely contribute to PCOS's development, suggesting a neuroendocrine origin.[22] It is thought that an overactive HPA axis is the main source of PCOS symptoms. This heightened exercise can cause androgen hormone levels to rise, GnRH secretion to increase, and cortisol turnover to accelerate. Women with PCOS are prone to heightened depression, anxiety, and appetite due to the psychological repercussions and HPA axis activation, which is necessary to release FSH and LH gonadotropins.[4]

Additionally, the stimulation of GnRH neurons with AMH increases their rate of discharge, which leads to greater LH secretion and reduced FSH output from the pituitary. High gonadotropin levels, mainly LH, can lead to an excessive amount of androgens,[23] which could worsen depressive symptoms,[14] signifying that raised androgen levels may be the cause of PCOS-related psychiatric issues.[24] All in all, there seems to be a clear connection between the intensity of depression symptoms and androgens.[13,24]

Studies have demonstrated the connection between cortisol and depression,[13] as well as anxiety being associated with low serotonin and high cortisol levels.[14] Research suggests that individuals with AN[11] and BED have an above-average amount of cortisol, regardless of depression.[14] In contrast, cortisol levels in individuals with bulimia nervosa (BN) were regular.[13]

As a result of PCOS patients' hyperinsulinemia, reactive hypoglycemia can be caused, which then leads to the secretion of hormones such as adrenaline and cortisol that may bring about heart palpitations, tremors, anxiety, and irritability, ultimately causing disturbed sleep.[10] To understand how these connections affect the dietary habits of individuals with PCOS further investigation is needed.[25]

Disruptions in the brain-gut axis: Gut-brain axis exploration has unveiled essential insights with impacts on gastroenterology and neurology, especially psychiatry. Any disruption in the digestive system's operation can affect the brain's hormonal and automatic responses. The interaction between the digestive system and the brain is known as the gut–brain axis (Figure 3). The intricate combination of gut-derived-peptides(GDPs), CNS, and the gut-brain axis is critical for PCOS growth, maintenance, aberrant pathways, and psychological components.[4] These linked GDPs play an important part in the source and development of ED.[14]

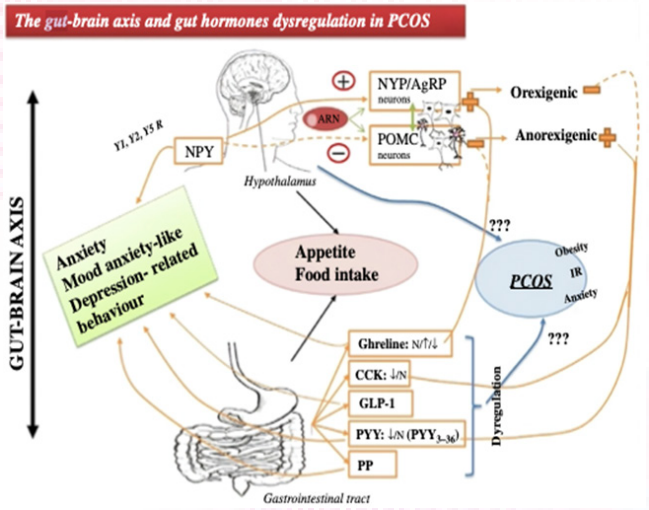

Figure 3. The gut -brain axis and gut hormones dys regulation in PCOS.[14]

Ghrelin,[4,14] cholecystokinin (CCK), and peptide YY(PYY) are important peptides for controlling eating and body weight.[4] It has been suggested that Glucagon-like peptides (GLP-1) and GLP-2, along with essential gut peptides, affect emotional-affective behavior. Evidence suggests ghrelin energizes behavior by stimulating the cholinergic-dopaminergic reward pathway. This link and hyperghrelinemia may provide a pharmacological treatment for binge eating.[4] On the contrary, studies showed that PYY encourages pleasurable behavior, as seen by the recognition that decreasing PYY intensifies depression-like features with no effect on anxiety. Moreover, PP, acting through Y4 receptors, may affect emotional-affective behavior. As for CCK, it has been linked to increased anxiety-like behavior in both humans and rodents. GLP-1 has reportedly been linked to heightened anxiety, while GLP-2 shown to lessen depression.[4] Lowering of CCK secretion may be linked to binge eating,[14] with decreased levels of CCK and ghrelin correlating to emotional and dietary issues in PCOS.[19] It has also been reported that appetite is impaired in women with PCOS, with alterations in hunger and gut hormones. A systematic review of 20 studies involving 894 women with and 574 women without PCOS reported lower ghrelin in PCOS (standardized mean difference -0.40; 95% confidence interval -0.73, -0.08), related to factors including insulin resistance.[26] In addition, research suggests women with PCOS tend to feel less full and hungrier after meals than women without PCOS, plus consuming more energy and hunger returning faster.[26] Other than ghrelin, all other gut hormones/peptides are usually associated with satiety.[27]

Eating Disorder in PCOS

Extensive research consistently shows a strong correlation between PCOS, disordered eating,[4,6,22,26] and the development of ED[24,26,28,29] in women. PCOS-related dietary changes, hunger, hyperinsulinemia, and obesity which present as disordered eating[14,30] can cause psychological problems such as anxiety, depression, cravings, overeating, and low self-esteem, and may be also caused by these psychological issues[14] (Figure 4).

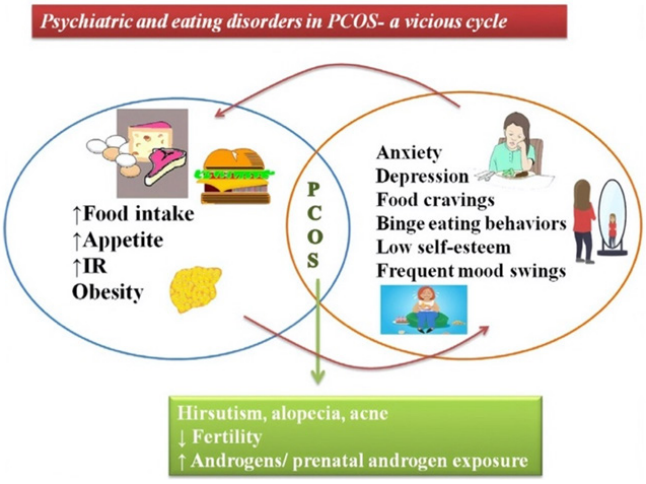

Figure 4. A vicious cycle of psychiatric and eating disorders in PCOS.[14]

A study of a meta-analysis established a high prevalence of depression and anxiety in PCOS sufferers, linked to elevated androgen and insulin levels.[12] In addition to these two essential elements, high stress raises cortisol, insulin, and androgen levels, resulting in depression and eating disorders due to their impact on mood and eating behavior.[13] These negative emotions increase the prevalence of disordered eating patterns.[31] Hyperandrogenism and hyperinsulinism commonly observed in PCOS women have greatly contributed to the development of eating disorders and abnormal eating habits in this population[18] (Figure 5).

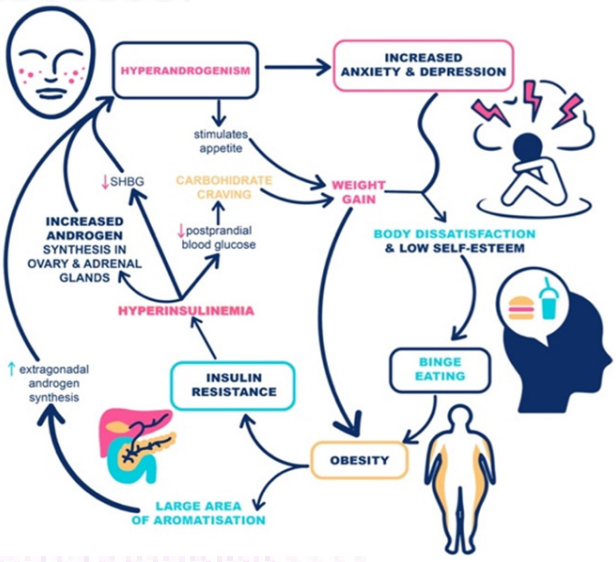

Figure 5 5Effects of hyper and rogenism and hyper insulinism on eating disorders in PCOS patients.[18]

According to research, high androgen levels may pose a heightened risk of BED[7,31] and BN.[28] These hormones may trigger bulimic behaviors through increased appetite[24,29] and decreased impulse control.[29] In actuality, compulsive overeating behaviors in PCOS patients with BED and BN are a way to cope with high stress.[13] PCOS patients who have BED often have elevated insulin levels, which can lower blood sugar thus stimulating hunger. Binge-eating impairs cognitive abilities and increases the likelihood of depression and anxiety.[31] Women with PCOS who have depression and anxiety are more likely to develop disordered eating than those without.[2] PCOS patients experience depression due to elevated androgen, insulin, and inflammation levels.[26] Research has revealed that high androgen levels are connected to more severe depression[12] and a fivefold increase in turbulent eating because of elevated anxiety.[2] Furthermore, a study suggests that hyperandrogenism may lead to a decrease in taste sensation in PCOS patients.[6] Elevated levels of testosterone, when combined with obesity, can often lead to intense hunger even when not hungry, potentially causing excessive eating and even eating-related issues.[29] PCOS, with its associated symptoms - acne,[8] hirsutism,[4,8] obesity, irregular periods, and infertility - has been linked to lower self-esteem[4,5] and body dissatisfaction, both of which can be causes of eating disorders.[5] Body image disturbance is a major factor in eating disorders, which can include irregular eating, restricted diets, and focus on body weight.[16] Excessive insulin and testosterone can spur an intense craving for carbs, signifying PCOS and BED[6] BED appears to be a factor in both obesity and disturbances in insulin regulation[7] Generally, fluctuating hormones during a menstrual cycle can influence food cravings and associated eating behavior[6] in PCOS women with ED.[30] Stress can cause a surge in appetite, resulting in overindulging and a higher Body Mass Index (BMI) in women with PCOS.[4] Nonetheless, it does not necessarily mean that all PCOS women are overweight/obese.[32] The frequency of overweight and obesity in patients frequently leads to disordered eating,[5] not just PCOS.[4] High BMI does not always imply an eating disorder, however, it may hint at low self-esteem[4] and physical distress that could alter eating habits.[4,5]

Research indicates genetic associations with serotonin, a neurotransmitter related to appetite, mood, and circadian rhythms, may be associated with disordered eating. Anorexia nervosa patients showed a drop in 5 HIAA levels, implying serotonin deficiency. This might result in a strict diet, as serotonin is created from tryptophan, an essential nutrient. Low serotonin and high testosterone in the brain may explain the aggressive behavior of those with eating disorders like BN. Research suggests testosterone modulates serotonin receptor activity, which impacts aggression, fear, and anxiety.[13]

BEDs are known to cause obesity which disrupts the appetite signaling system controlled by leptin and ghrelin hormones. Leptin, a hunger-reducing substance, had a major effect on hunger and fullness when administered in high doses to rodents, leading to decreased food consumption. However, the impact of leptin was short-lived, as the rodents displayed signs of resistance after two weeks, likely due to overproduction. Leptin affects reproductive processes through its effect on the hypothalamic-pituitary-ovarian (HPO) axis. Excess levels of leptin in overweight individuals may influence ovarian functioning.

Females afflicted with BN demonstrate a decreased sense of self-worth, a psychological factor, that may prompt them to be displeased with their physical form. Individuals who show intensified levels of anxiousness and depressive symptoms are prone to using disordered eating as an ineffectual way of dealing with their emotions. It is theorized that the adrenal hormones, notably cortisol and DHEA, increase in a depressive episode, and DHEA may have neuroprotective capabilities in the brain, restraining cortisol from damaging neurons and lessening the probability of developing psychopathology, and may even have a direct effect on depression. Imbalanced convictions about weight, body shape, and consumption are pivotal in the development and perpetuation of eating disorders.[12] To sum it all up, severely heightened eating disorders can drastically reduce the quality of life to a very alarming degree.[16]

COMPARISON BETWEEN ED TYPES & THEIR PREVALENCE

Table 1: shows the comparison between different types of eating disorders.

	BN	AN-BP	BED	OFSED
Age group	15-19 years and 20s	13-19 years and 20s	≥20 years	12-25 years
BMI status	>19.0 kg/m²	<17.5 kg/m²	>19.0 kg/m²	May not meet the BMI requirements
Compensatory behavior	Present	Present	May be present	Frequency of behaviors
Fear of weight gain	May be present	Present	May be present	
Distinctive features	Recurrent episodes of binges	Distortions in perceptions of weight/ size	-Associated with physical comorbidities -Binge eating episodes -Obese	Difficulty capturing its heterogenous nature

The most common eating disorder observed in women with PCOS is BED[4] No AN-BP diagnosis was observed in PCOS individuals.[4] A meta-analysis investigation revealed that there was no statistical relationship between PCOS and AN-BP. Both AN and PCOS cause patients to have abnormal eating habits and fluctuating weight, but there is a contrast between the two; PCOS is more common in women with normal or increased BMI, whereas AN is more common in underweight women. Furthermore, the same study discovered a link between PCOS and other types of eating disorders such as BN, BED, and any other ED.[25]

In a study conducted, researchers noted the prevalence of diagnosed EDs in PCOS patients. Results varied between diagnostic categories, with estimates for AN ranging from 0.0% to 1.3%, for BN ranging from 0.0% to 12.6%, for BED ranging from 4% to 15%, and one research reporting a frequency of 22.5% for EDNOS.[31]

DIFFERENCES BETWEEN DISORDERED EATING AND EATING DISORDER

Disordered eating is a condition that shares the same symptoms as an eating disorder but with a reduced frequency or degree of severity.[4,26,33] As explained earlier in this review, an eating disorder is a psychological disorder with abnormal eating behaviors.[26] Body image disturbances, anxiety towards specific food types, distorted perceptions, and low self-esteem based primarily on body weight have all been linked to disordered eating practices in PCOS patients.[4,16,26] Disordered eating appears to be used as a functional and emotional management technique by people who experience higher levels of anxiety and depressive symptoms.[2,5,11,12] In several studies examined, authors reported that when comparing PCOS patients to controls, disordered eating, but not eating disorders, were more common.[4,26] Different studies suggested different findings. One of them showed that the diagnosis of an eating disorder did not differ substantially between women with and without PCOS,[4] whilethe other collective study suggested an increased risk of both disordered eating and eating disorder in PCOS patients.[2] This is relevant because many women will report symptoms of disordered eating that are linked to discomfort and impairment, but they do not meet the diagnostic criteria for a particular ED diagnosis.[31] Furthermore, an earlier meta-analysis found that women with PCOS had a 3.05 odds ratio (OR) for disordered eating behavior when compared to those without.[4,31] To state another known relationship, after controlling for age and BMI in women with PCOS, a link was found with psychiatric comorbidities such that the presence of anxiety increases the likelihood of disordered eating by about fivefold,[2,34] and persistent weight gain over the follow-up period was also discovered.[11] It's interesting to note that the diagnosis of PCOS did not predict either the presence of disordered eating or the diagnosis of an eating disorder.[4] Irrespective of PCOS status, older ageand higher BMI increased the probability that women would engage in disordered eating behavior, whereas younger age and higher BMI increased the odds that women would be diagnosed with an eating disorder.[4] The cause of disordered eating in women with PCOS is unknown, however, it is believed to be influenced by several variables such as: higher BMI, weight, eating concerns,body dissatisfaction, anxiety, and higher diet restraint.[4,5]

The present evidence on either disordered eating or comprehensive ED diagnoses in women with PCOS suggests a significantly elevated risk.[34] However, in most of the articles, women with PCOS had more disordered eating behaviorsthanED.[4]

DIAGNOSTIC METHODS

PCOS

Rotterdam Criteria: According to the Rotterdam consensus, polycystic ovarian syndrome (PCOS) is diagnosed by the presence of two or three of the following criteria: 1) hyperandrogenism (clinical or biochemical) 2) oligo-anovulation 3) an ultrasound examination of polycystic ovaries.[3]

Eating Disorder

Eating disorder examination questionnaire (EDE-Q): The EDE-Q is a self-reported 28-item questionnaire and has the purpose of evaluating the range, regularity, and severity of behaviors used for the assessment of ED. The EDE-Q yields data loading on four subscales – Weight Concern, Shape Concern, Eating Concern, and Dietary Restraint as well as a Global score.[4,17]

The EDE-Q is the advised clinical gold standard screening instrument to evaluate the presence of essential cognitive and behavioral traits prevalent in both disordered eating and eating disorders.[4]

Diagnostic and statistical manual of mental disorders (DSM-5): It provides information on five different varieties of OSFED, including atypical AN, BN (of low frequency and/or limited length), BED (of low frequency and/or limited duration), purging disorder, and night eating syndrome.[30]

Eating attitudes test (EAT-26): The EAT-26 is perhaps the most extensively used standardized self-report assessment of eating disorder symptoms and concerns. It is a 26-item test that measures the concern about aberrant eating. A 6-point Likert scale was used by participants to rank each issue. Higher ratings indicating greater eating disorders.[8]

Demographics Questionnaire

A demographics questionnaire was utilized to gather background data, anthropometric measurements (such as height and weight), participant history, and eating disorder disclosure patterns.[17]

RACIAL DIFFERENCES

In one of the studies, the researchers correlated EDE-Q scores with behaviors of PCOS phenotypes. Similar comparisons were done across racial groups, defined as white vs. nonwhite, and then broken down into the following racial backgrounds in an exploratory analysis: "white", "black", "Asian", "Hispanic" or "mixed". There were notable disparities in EDE-Q scores between white and nonwhite women with PCOS. Nonwhite women exhibited higher global EDE-Q scores, thus indicating a greater burden of ED symptoms. Except for restraint, nonwhite women had greater subscale ratings than white women. Meanwhile, they found no difference in ED behavior rates between racial groups. In an exploratory analysis, they further classified race into white, black, Asian, Hispanic, and mixed racial groupings. Groups like black, Hispanic, and mixed women had higher EDE-Q global and subscale scores than white women; whereas, Asian women scored lower than white women. Cultural variations likely contribute to ED risk in many ways, such as through media, eating patterns, or beauty norms. Interconnected socioeconomic factors may also muddle the impact of race. Additional research is needed to determine whether and how race influences ED symptom risk in PCOS to develop culturally competent therapies in the future.[11]

FINDINGS

ED are more prevalent in women with PCOS. The frequency of eating disorders is substantially connected with amenorrhea ($p<0.001$) and oligomenorrhea ($p<0.001$),

according to a study conducted in Sweden on 11,503 women.[34] Researchers observed a high prevalence of BN, BED, and NES among the PCOS group using DSM-5 criteria, and the ED scores were noticeably higher for shape and weight worries.[34] They have also found a negative connection between EDE-Q global scores and PCOS screening test scores for health-related quality of life (HQoL).[34] Women with PCOS reported noticeably greater symptoms of anxiety and depression than controls and had low values in the measurement technique (HQoL) unlike the EDE-Q scores. Women with PCOS scored higher on the EDE-Q than a normative sample and reported that baseline measurements of hyperandrogenism, depressive symptoms, and BMI all predict disordered eating attitudes and behaviors.[11]

BED: A meta-analysis of four studies that included 868 participants revealed a statistically significant link between PCOS and a clinical diagnosis of binge eating disorder. (OR, 2.95; 95% CI, 1.61-5.42, I2=18.9%).[25]

BN: A meta-analysis of five trials with a total of 269,212 participants revealed a statistically significant link between PCOS and a clinical diagnosis of bulimia nervosa (OR, 1.37; 95% CI, 1.17-1.60; I2=0%). Utilizing multiple scales, three investigations with 458 individuals examined bulimia nervosa symptoms. Patients with PCOS performed better on these scales than patients without the condition. (standardized mean difference,1.25; 95% CI, 0.20-2.29; I2=95.1%).[25]

AN: A meta-analysis of three studies involving 268,417 participants found no statistically significant link between PCOS and anorexia nervosa. (OR, 0.92; 95% CI, 0.78-1.10; I2=0%).[25]

Any eating disorder:A meta-analysis of four research involving 7188 patients revealed a statistically significant link between PCOS and any clinically diagnosed eating disorder. (OR, 3.68; 95% CI, 1.38-9.81, I2=4 4. 5%).[25]

MANAGEMENT AND TREATMENT

For PCOS populations to experience the best physical results, early and accurate detection of binge eating symptoms is crucial,[30] also in order to rule out any mood or ED, women with PCOS would most likely need a full psychiatric evaluation.[19,36,37] The 2018 guidelines from the Androgen Excess-PCOS Association recognize the clinical importance of this problem and promote screening[2,5,35] for disordered eating in all PCOS-afflicted women.[30] Furthermore, it is critical to raise awareness[16] and educate women about disordered eating in PCOS, as many women with EDs get misdiagnosed and are unaware that their eating and weight-related beliefs and behaviors are abnormal and cause discomfort.[30]

The mainstay of PCOS treatment for women is a change in lifestyle.[2,4,38-40] It would be critical to monitor PCOS women's diet to aid with the symptoms caused by an excess of androgens and insulin resistance, as well as to reduce the risk of diabetes and heart disease later in life.[16,26,30,38] Several prospective studies have established that dieting predicts future bulimic symptomatology, and it is evident that when BN is present, treatment referral should focus on resolving the core BN symptoms rather than on weight loss.[15,34] Although these treatments have not yet been tested on PCOS women who also have eating disorders, it is anticipated that such an approach to weight management would be more effective than focusing solely on weight management because it would also address the main psychological factors underlying EDs.[4,31]

CONCLUSION

As a result of, clinicians should consider chronic psychological distress and eating disorders as significant factors when diagnosing PCOS. Furthermore, a comprehensive evaluation of eating behaviors and dietary patterns in females with PCOS is essential. Consequently, investigating the connection between PCOS and eating disorders holds great potential for improving the overall care and well-being of affected individuals.

ETHICAL DECLARATION

Referee Evaluation Process: Externally peer-reviewed.

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