Polycystic Ovary Syndrome and Infertility: A Retrospective Cross-Sectional Study

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Abstract

Background: Polycystic ovary syndrome (PCOS) is the most common endocrinological and reproductive-metabolic disorder in women, characterized by chronic ovulatory dysfunction, oligomenorrhea, hyperandrogenism and infertility. Infertility, the absence of a desired pregnancy with regular, unprotected intercourse for a period of at least one year, is a major public health problem today.

Aim: The aim of this retrospectively registered study was to examine the hormonal characteristics of infertile patients diagnosed with PCOS and compare them with a control group of infertile women not diagnosed with PCOS, of comparable ages and body mass indices.

Methods: In this retrospective cross-sectional study, the subjects were thirty patients diagnosed with PCOS treated for infertility at the Department of Obstetrics and Gynecology, Sveti Duh Clinical Hospital, who were compared to a control group of women not diagnosed with PCOS but diagnosed with infertility, of comparable ages and body mass indices. The data were collected from an electronic database, and the values of the observed indicators of the patients' health status were presented in graphs and tables.

Results: The results show that there were statistically significant differences in the levels of AMH, LH, E2 and FSH. In other words, the patients with PCOS had higher AMH and LH, and lower E2 and FSH, in comparison to women not diagnosed with polycystic ovaries of the comparable age and body mass indices. TSH and prolactin levels were comparable between the two groups.

Conclusion: Our study confirmed that infertile patients diagnosed with PCOS have different serum levels of pituitary and ovarian sex hormones in comparison to the controls.

Keywords: Polycystic ovary syndrome, infertility, hormones

Introduction

Polycystic ovary syndrome (PCOS) is a common health disorder in women, characterized by chronic ovulatory dysfunction, oligomenorrhea, hyperandrogenism and infertility. Infertility could be defined as the absence of a desired pregnancy with regular, unprotected intercourse for a period of one year (1). PCOS is the most common endocrinological and reproductive-metabolic disorder in women, which can be the result of abnormal interaction among various behavioral, environmental and genetic factors (2). Recently, there has been increased interest in the field of PCOS research.

Hyperandrogenism, which refers to an elevated level of endogenous androgens, is one of the main features of PCOS that affects many patients. It is associated with the appearance of hirsutism, acne and androgenic alopecia (3). Hirsutism is excessive hairiness in women in places where hairiness is normally characteristic for men (4). After hirsutism, acne and oily skin are also found in almost 15–25% of women with PCOS (3). Acne is a chronic inflammatory skin disease that affects the seborrheic areas (face and upper body), and is characterized by the appearance of comedones, inflammatory lesions and scars (3). In addition to hirsutism and acne, androgen-dependent hair loss called androgenic alopecia also occurs but is less prevalent (5).

Polycystic ovaries are furthermore characterized by cycle disorders, mainly caused by anovulation and characterized by long cycles, amenorrhea, irregular bleeding that can be heavy or light, bleeding between periods and postcoital bleeding (6).

The National Institutes of Health define PCOS as unexplained hyperandrogenic anovulation. A medical diagnosis of PCOS can be established in the presence of the following criteria: androgen excess and infrequent ovulation with the exclusion of other disorders having similar clinical symptoms (7). According to the Rotterdam criteria, PCOS is defined if two of the following three parameters are present: 1. oligo-anovulation and/or anovulation with consequent oligo-amenorrhea or amenorrhea, 2. biochemical and/or clinical indicators of hyperandrogenism and/or hyperandrogenemia, 3. polycystic appearance of ovaries confirmed by ultrasonography, after the exclusion of related diseases (8).

The aim of this study was to inspect the hormonal characteristics of infertile women diagnosed with polycystic ovaries (PCOS) and compare them with a control group of infertile women without such a diagnosis, of comparable ages and body mass indices.

Matherials and Methods

Study design

We conducted a retrospective observational cross-sectional study.

Ethics

This study was approved by the Ethics Committee of the Sveti Duh Clinical Hospital, Zagreb, Croatia, under no. 01-03-1014/7, and has been performed in accordance with the principles of the Declaration of Helsinki.

Place and time conducted

The study was conducted at the Department of Obstetrics and Gynecology at the Sveti Duh Clinical Hospital from April to June 2022. During that period, data were collected on the patients who were treated in the Department during 2021.

Eligibility criteria

The subjects were thirty patients diagnosed with polycystic ovaries being treated for infertility at the Department of Obstetrics and Gynecology at the Sveti Duh Clinical Hospital, compared with a control group of women (N=15) not diagnosed with PCOS, of comparable ages and body mass indices (excluding ovarian insufficiency).

Data extraction

For this study, we collected data from an electronic database. We searched the medical records within the hospital medical program while coding the names so that the identities of the patients were kept confidential. We analyzed the serum levels

of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), anti-müllerian hormone (AMH), thyroid-stimulating hormone (TSH) and prolactin. Serum hormone levels were measured from blood samples collected in the early follicular phase, from the 2nd to the 4th day of the cycle, during the course of infertility treatment.

Data analysis

The values of the observed indicators of the patients' conditions are presented in graphs and tables.

Descriptive statistics methods, namely the arithmetic mean as the mean value and the standard deviation as an indicator of deviation from the mean value, were used.

The normality of the distribution had been previously tested using the Kolmogorov-Smirnov test, while the difference between the observed groups was tested using the *t*-test for independent measurements.

Analysis was performed using the statistical software STATISTICA 12.

Results

The level of FSH was statistically significantly lower in the infertile patients with polycystic ovary syndrome compared to the infertile patients in the control group not diagnosed with polycystic ovaries (t=1.66; P=0.05).

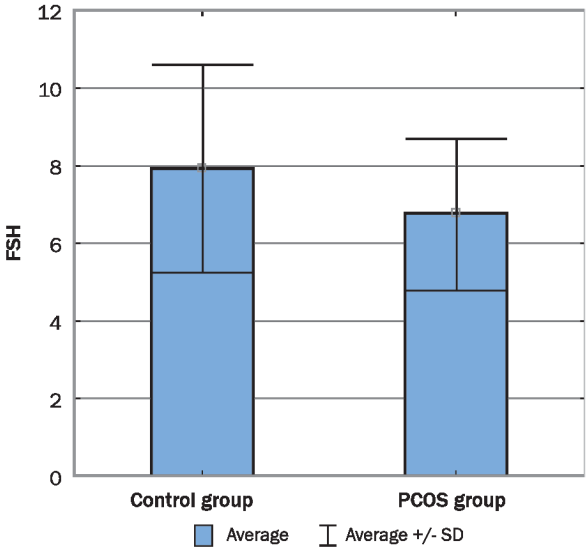

Figure 1. *Distribution of the results of the comparison of the serum FSH levels in infertile patients with and without diagnosed polycystic ovaries*

The level of LH was statistically significantly higher in the infertile patients with polycystic ovary syndrome compared to the infertile patients in the control group not diagnosed with polycystic ovaries (t=2.08; P=0.043).

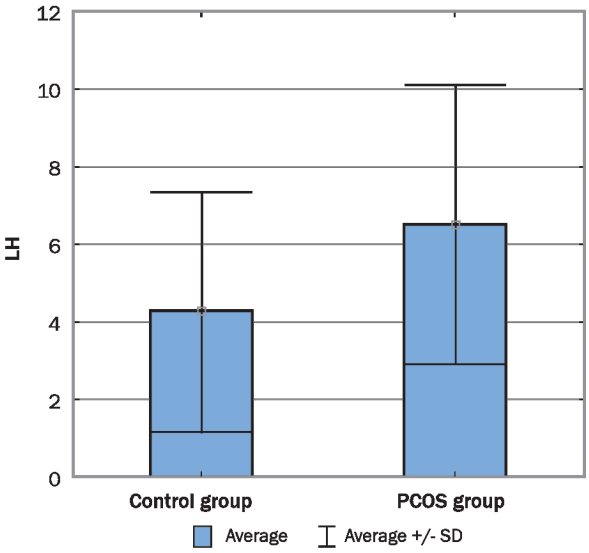

Figure 2. *Distribution of the results of the comparison of the serum LH levels in the infertile patients with and without diagnosed polycystic ovaries*

The level of E2 is statistically significantly lower in infertile patients with polycystic ovary syndrome compared to infertile patients in the control group without diagnosed polycystic ovaries (t=2.50; P=0.017).

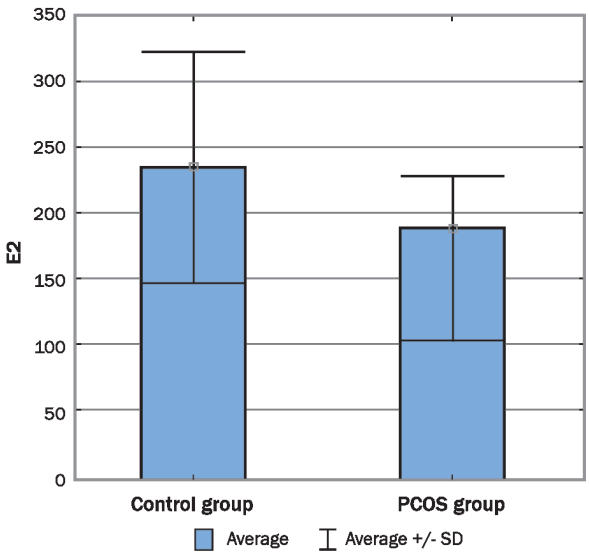

Figure 3. *Distribution of the results of the comparison of the serum E2 levels in the infertile patients with and without diagnosed polycystic ovaries*

The level of AMH is statistically significantly higher in infertile patients with polycystic ovary syndrome compared to infertile patients in the control group without diagnosed polycystic ovaries (t=4.55; P<0.001).

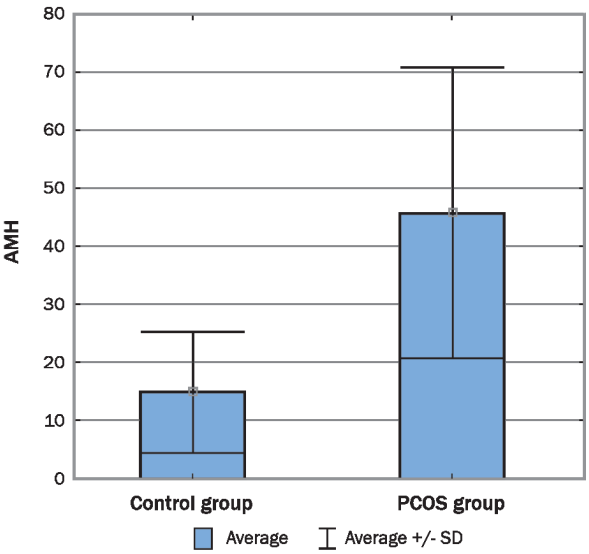

Figure 4. *Distribution of the results of the comparison of the serum AMH levels in the infertile patients with and without diagnosed polycystic ovaries*

The TSH level in the infertile patients with polycystic ovary syndrome was comparable to the control group of infertile patients without diagnosed polycystic ovaries, with no statistically significant difference (t=4.41; P=0.166).

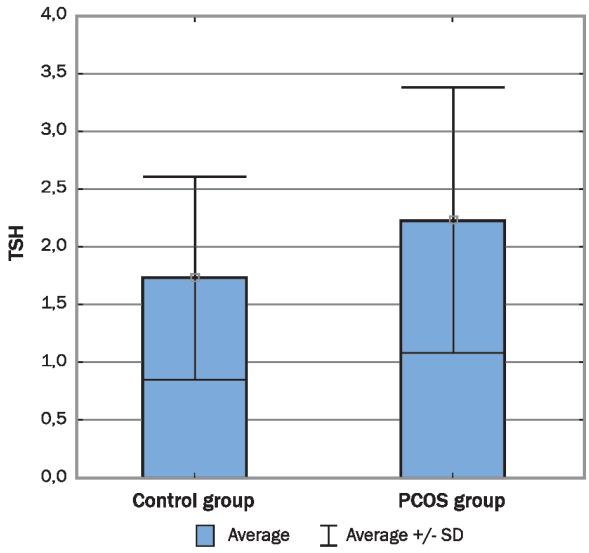

Figure 5. *Distribution of the results of the comparison of the serum TSH levels in infertile patients with and without the diagnosis of polycystic ovaries*

The level of PRL in the infertile patients with polycystic ovary syndrome was comparable to the control group of infertile patients not diagnosed with polycystic ovaries, with no statistically significant difference (t=0.49; P=0.628).

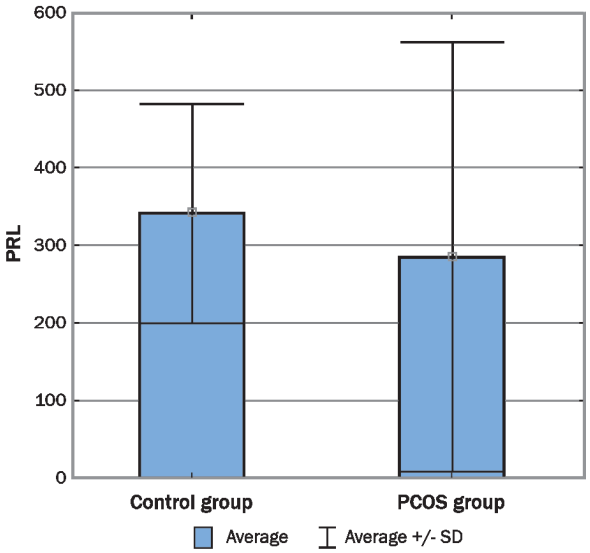

Figure 6. *Distribution of the results of the comparison of the serum PRL levels in the infertile patients with and without polycystic ovaries*

The mean duration of infertility among the patients with polycystic ovaries was not statistically significantly different from the control group (t=0.81; P=0.420).

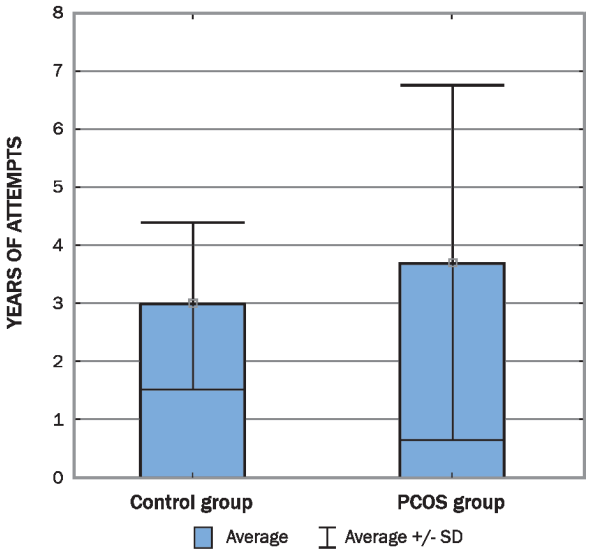

Figure 7. *Distribution of the results of the comparison of the duration of infertility in the infertile patients with and without diagnosed polycystic ovaries*

The mean age of patients with polycystic ovaries was comparable to that of the control group, with no statistically significant difference.

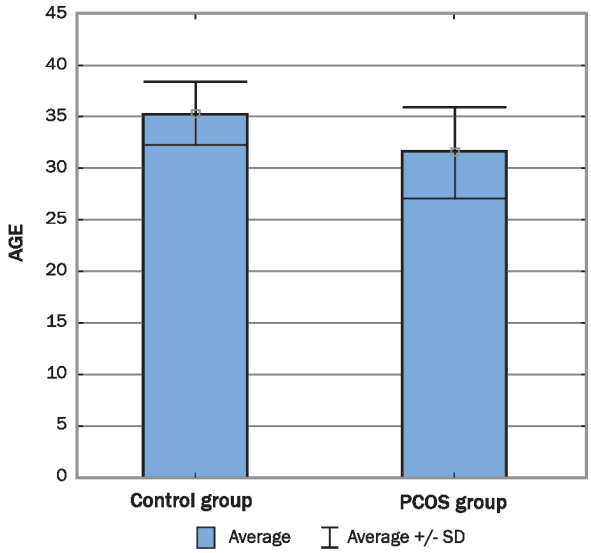

Figure 8. *Age distribution in the group of patients with PCOS, as compared to the controls*

Discussion

Polycystic ovary syndrome (PCOS) is a common endocrinopathy characterized by oligo-ovulation or anovulation, signs of androgen excess and a polycystic appearance of the ovaries on ultrasound imaging. These signs and symptoms vary widely throughout a lifetime. In patients diagnosed with PCOS, clinical signs often include menstrual cycle abnormalities, infertility, androgen excess and other endocrine dysfunctions (8). Symptoms of PCOS most often become apparent with the appearance of the first menstrual bleeding.

Infertility is defined as the inability to conceive after 1 year of regular unprotected intercourse for women under 35 years of age or after six months for women over 35. Published data in large studies claim that the chance of conception each month is 20-25% (9). When trying to conceive, the chance that a woman will become pregnant in 3 months is about 50%, the chance that she will conceive in 6 months is 75%, and during a year of trying to conceive, the chance that a woman will become pregnant is more than 85% (9, 10). However, well-publicized successes in the treatment of infertility give patients greater hope that medical intervention can help them achieve their goal.

The results showed that the FSH level was lower among the patients with polycystic ovaries compared to those in the control group (Figure 1). On the other hand, LH levels were significantly higher in the PCOS group as compared to the controls (Figure 2). This confirmed the hypothesis of differences in hormone levels between the control and PCOS groups.

The indicator and first sign of ovarian reserve is the procedure of measuring serum values of follicle-stimulating hormone (FSH) during the early follicular phase (11). As ovarian function declines, the supporting cells (granulosa cells and luteal cells) secrete less inhibin, which is responsible for inhibiting the secretion of FSH by the pituitary gland. With the loss of luteal inhibin, FSH levels rise in the early follicular phase, and a value > 10 mIU/mL indicates a significant loss of ovarian reserve, requiring more rapid evaluation and intensive treatment. In a study dealing with judgments and analyses of IVF cycles, a serum FSH value greater than 15 mIU/mL served as a predictor of a reduced pregnancy rate (11).

Malini et al. grouped subjects with PCOS into seven subcategories with regard to the pattern of LH rise in relation to FSH levels, i.e., how many times the LH level is higher than the FSH level. Sixty of the test subjects were women with normal ovulation, and the different subcategories were PCOS with the same LH and FSH levels and with variable ratios of LH and FSH levels (12).

In Saadia's investigation conducted from 2018 to 2019, LH levels were studied in 63 patients diagnosed with PCOS but with different body mass indices and these LH levels were compared in patients with low or high body mass indices (2). It was thereby confirmed that there is no significant difference between LH values in patients diagnosed with PCOS with high or low body mass indices, so it was concluded that body mass index is not correlated with LH levels (2).

Furthermore, a study conducted by Fakhoury H. et al. observed the influence of age and

body mass index on serum hormone values. The sample for the study was 62 patients with PCOS and 40 women in the control group without PCOS (13). Their conclusion also confirmed the hypothesis of this study. Serum LH values were higher in the group of patients with PCOS than in the control group of healthy women, regardless of age or body mass index (13).

Our results also showed that the level of E2 in the patients diagnosed with polycystic ovaries is lower compared to patients in the control group (Figure 3). The hypothesis of differences in the level of sex hormones between infertile patients diagnosed with polycystic ovaries and those without was confirmed.

In a study carried out by Daghestani MH. et al., the authors observed metabolic profiles in obese patients with and without PCOS (14). Contrary to this study, their data describe a higher level of E2 in obese patients with PCOS with a mean value of 217, compared to obese women without a PCOS with a mean value of 143 (14). It should be noted that the studies by Daghestani MH. et al. indicated increased insulin resistance in obese women compared to women of normal weight. Taking into account that both studied groups were obese, the conclusion was suggested that PCOS does not play a role in increasing insulin resistance (14). Several studies that have noted that most PCOS patients show an abdominal form of obesity, and that increased visceral fat may be a cause or an early consequence of insulin resistance in obese PCOS patients, which support the proposed conclusion.

The results showed that the mean level of AMH was higher among patients with polycystic ovaries compared to patients in the control group (Figure 4). This confirmed the hypothesis of a different value of AMH in infertile patients with PCOS compared to infertile patients without such a diagnosis, of comparable age and body mass index. A typical polycystic ovary normally contains two to three times more preantral and antral follicles compared to a normal ovary (15). Within the granulosa cells of these developing follicles, the dimeric glycoprotein antimüllerian hormone (AMH) is produced, and serum AMH levels correlate closely with the number of antral follicles. It is convincing that AMH serum values are two to three times higher in women diagnosed with PCOS, in contrast to the control group of women without PCOS (16, 17). For this reason, some see AMH as a potentially useful diagnostic marker for PCOS (18). Documented reports referring to AMH as a marker in PCOS are still lacking and further research is required before it can be accepted as a formal, established diagnostic criterion (19).

Analyzing the literature, it should be noted that the studies cover different populations, use different sets for measuring AMH and have different cut-off values for androgen concentrations and body mass index. These and other factors, such as the small sample size and retrospective study design, probably influence the fact that AMH is not yet used as a definitive diagnostic marker of polycystic ovary syndrome. Due to the possible heterogeneity of the results and differences arising from the study population, serum AMH levels should not be used as the sole test for the diagnosis of PCOS. A cut-off value of 35 pmol/L has been proposed to differentiate women with PCOS from healthy women. A study conducted by Rudnick E. et al. showed that serum AMH values are higher in adolescents with PCOS, with an increase in antral follicles and ovarian size compared to adolescents without PCOS (20).

The results from our study showed that the level of TSH was comparable in infertile patients with polycystic ovary syndrome to that of infertile patients in the control group (Figure 5). However, there was no statistically significant difference in serum TSH levels between the observed groups.

Fatima M. et al. studied the association between subclinical hypothyroidism (SCH) and polycystic ovary syndrome to determine the correlation between SCH and PCOS together with the impact of SCH on metabolic and hormonal parameters in women with PCOS (21). The results showed a significant difference in weight, body mass index, insulin, homeostatic model assessment of insulin resistance (HOMA-IR) and TSH levels in the SCH group, compared to the control group.

An exceptional correlation was observed between serum TSH levels and hip-to-waist ratio, body weight, body mass index, insulin and judgment of insulin resistance according to the homeostatic model (HOMA-IR) in patients with PCOS (21).

Our results also showed that the level of PRL was comparable in infertile patients with polycystic ovary syndrome and infertile patients in the control group (Figure 6). However, there was no statistically significant difference in serum PRL levels between the observed groups. Davoudi Z. et al. evaluated serum prolactin levels in 330 patients with PCOS and compared clinical features and hormone levels between patients with hyperprolactinemia and normal prolactin levels (22). Prolactin values were determined to be normal if their values were equal to or less than 25 ng/ml, but if prolactin values were >25 ng/ml, then the patients were subjected to further tests to rule out macroprolactinemia (22). In the case of hyperprolactinemia, an MRI of the brain was performed in order to detect a pituitary adenoma. Furthermore, higher LH levels and LH/FSH ratios, as well as lower estradiol levels, were observed in patients with normal prolactin levels. In addition, disturbances in menstrual cycles were present in patients who had pituitary adenomas (22). Davoudi Z. et al. also found no significant differences between the examined groups with regard to age and body mass index (22).

Delcour C. et al. clarified hypothetical epidemiological links between PCOS and hyperprolactinemia through a critical and updated review of the available literature on this topic (23). They showed that the link between hyperprolactinemia and PCOS comes from old studies in which PCOS was diagnosed according to the criteria of the time and in which hyperprolactinemia was insufficiently investigated. They also provided confirmatory information about data from the literature that did not suggest the existence of hyperprolactinemia in correlation with PCOS (23).

Another study by Hayashide et al. showed that increased prolactin levels were most frequently correlated with the presence of macroprolactin in women with polycystic ovaries, indicating that prolactin evaluation is therefore necessary (24). This first step is essential in order to avoid misdiagnosis and the unnecessary prescription of pituitary MRI.

Bearing all the above in mind, it is important to stress that the patients in our study were comparable regarding all epidemiologic characteristics, such as chronological age, duration of infertility, body mass index and age (Figures 7 and 8).

The results showed different hormonal characteristics of infertile patients with established PCOS as compared to controls treated for infertility at the Department of Obstetrics and Gynecology, Sveti Duh Clinical Hospital in Zagreb.

A limitation of this study was the small sample size, considering the fact that polycystic ovary syndrome affects a relatively large number of women. The retrospective design of the study may also have influenced the results. Future work should also include data on OGTT, insulin levels and body mass index, since they all could influence the measured hormone levels and PCOS phenotype.

Conclusion

Our research confirmed that infertile patients diagnosed with PCOS have different serum levels of pituitary and ovarian sex hormones as compared to controls. This could have implications in the evaluation of the hormone levels in patients with PCOS.

Declarations

Aknowledgements

This study was part of Nada Gruja's Master of Nursing thesis, originally written and defended in the Croatian language.

Authors' contributions

NG contributed to the study design, statistical analysis, interpretation of the data and the drafting of the manuscript. ATL contributed to the study design, data analysis and manuscript review. Both authors have read and approved the final version of the manuscript.

Ethics consideration

This study was approved by the Ethics Committee of the Sveti Duh Clinical Hospital, Zagreb, Croatia, under no. 01-03-1014/7, and has been performed in accordance with the principles of the Declaration of Helsinki.

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Competing interests

The authors declare that they have no competing interests.

Data sharing statement

Data available on request from the authors.

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