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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии
საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

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GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman (Кириллица)**, для текста на грузинском языке следует использовать **AcadNusx**. Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - <http://www.spinesurgery.ru/files/publish.pdf> и http://www.nlm.nih.gov/bsd/uniform_requirements.html В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректур авторам не высылаются, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or computer-printed on a single side of standard typing paper, with the left margin of 3 centimeters width, and 1.5 spacing between the lines, typeface - **Times New Roman (Cyrillic)**, print size - 12 (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf

In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

**Articles that Fail to Meet the Aforementioned
Requirements are not Assigned to be Reviewed.**

ავტორთა საქურაღებოლ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დაიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx**. შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შედეგის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფხიხლებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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CLINICAL AND ENDOCRINE ALTERATIONS IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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Abstract.

Polycystic ovary syndrome (PCOS) is the most prevalent endocrine disorder that affects women of reproductive age.

Aim: To determine the association between body mass index (BMI), hirsutism, acne, and hormonal status with PCOS.

Materials and Methods: This cross-sectional study included 55 women with PCOS, between the ages of 18 and 39 who attended the Obstetrics and Gynecology Clinic at the University Clinical Center of Kosovo (UCCCK). BMI was calculated and luteinizing hormone (LH), follicle stimulating hormone (FSH), LH/FSH ratio, testosterone and dehydroepiandrosterone sulfate (DHEA-S) values were determined. All the data were analyzed after the clinic-endocrine profile was assessed.

Results: The average age of women with PCOS was 21.36±4.29. Hirsutism and acne were quite conspicuous, as well as testosterone and DHEA-S values. Moreover, women with PCOS had higher values of LH and LH/FSH ratio (8.17±9.66 and 2.86±2.74) but not FSH values (4.16±2.97) that showed a positive correlation with polycystic ovary syndrome.

Conclusion: Thus, PCOS is a multifaceted endocrine and metabolic disorder, which needs early recognition and treatment to prevent long-term complications.

Key words. PCOS, LH/FSH ratio, testosterone, DHEA-S.

Introduction.

Polycystic ovary syndrome (PCOS) is a chronic condition, that usually starts during adolescence, but symptoms may fluctuate over time [1]. PCOS can cause hormonal imbalances, irregular periods, excess androgen levels and cysts in the ovaries. It increases women's risk for infertility, endometrial cancer, late menopause, and also metabolic abnormalities, including insulin resistance, type 2 diabetes mellitus, dyslipidemia, and cardiovascular disease [1-4]. The prevalence of PCOS may vary further depending on the diagnostic criteria and definitions used, and ranges from 6% to 20% in all women [5].

Studies show an association between PCOS and body mass index (BMI), where most women afflicted by PCOS are overweight or obese [6]. Furthermore, there is a link between PCOS and the genetic basis. This interrelation was first reported by Cooper and colleagues in 1968. Studies in mono- and dizygotic twins also showed the influence of genetic basis with estimated 72% variance in risk of PCOS [7]. Oral contraceptive pills along with other treatments are used as a first-line therapy for concurrent treatment of menstrual irregularity, acne, and hirsutism in women with polycystic ovary syndrome (PCOS), thus playing an important role in the symptom management of the PCOS women. [8,9].

Acne vulgaris is one of the most frequently encountered, externally visible skin disease in dermatology for individuals between 15 and 40 years of age. Hyperandrogenism is associated with increased acne development and is often the first indicator in the appearance of acne. Hyperandrogenism is one of the metabolic changes that accompany PCOS, therefore it is also a main cutaneous manifestation of the syndrome [10].

Abnormalities in the neuroendocrine system stimulating the pituitary for excessive production of luteinizing hormone than that of follicle-stimulating hormone is seen in PCOS women. Excess LH stimulates ovarian androgen production, whereas a relative deficit in FSH impairs follicular development. The imbalance in the LH/FSH ratio ultimately leading to hyperandrogenism in PCOS women [11,12].

There are two primary sources of androgenic hormones in women: the adrenal glands, and the ovaries. The adrenal gland is responsible for producing dehydroepiandrosterone sulfate (DHEA-S) and makes up on average 25% of our overall androgen production. The ovaries, on the other hand, are responsible for producing testosterone. In women with PCOS studies show elevated levels of testosterone and DHEA-S in the bloodstream [13,14].

Consequently, the aim of this study was to investigate the association of BMI, hirsutism, acne, and hormonal status with PCOS.

Materials and Methods.

This cross-sectional study was conducted in the Obstetrics and Gynecology Clinic at University Clinical Center of Kosovo (UCCCK) between April and December 2022, and was approved by the Ethics Committee of the UCCCK, Prishtina, Kosovo (ref. No.:1055/22). Informed consent was obtained from all participants. The study involved 55 women between 18-39 years old. The diagnosis of PCOS was based on the Rotterdam criteria [15] with at least two of the following three criteria present: the existence of oligomenorrhea, clinical or biochemical hyperandrogenism, and polycystic appearance of the ovaries on ultrasonography. Ultrasonography was performed by a specialist of obstetrics and gynecology. Polycystic ovaries on ultrasonography were identified according to the criteria of Adams, i.e. 10 or more cysts, usually arranged peripherally, of diameter 2-8 mm, associated with an increase in ovarian stroma and volume [16,17].

Other causes of hyperprolactinemia, congenital adrenal hyperplasia, hypothyroidism, and subjects taking any drugs or supplements in the last 6 months were excluded from the study. Smoking and alcohol abuse were also among the exclusion criteria.

Participants were asked about menstrual disorders and were examined for weight, height, hirsutism, and acne. BMI was calculated as weight in kilograms divided by the square of height in meters. Acne was identified according to the Investigator Global Assessment of Acne (IGA), whereas hirsutism was defined using a modified Ferriman-Gallwey method (mFG). An mFG score of ≥ 8 was considered hirsutism [18,19]. Patients were tested for follicle-stimulating hormone (FSH), luteinizing hormone (LH), LH/FSH ratio, testosterone and DHEA-S. Serum was collected according to the routine procedure: after an overnight fast during the follicular phase (within 3 and 5 days of the menstrual cycle). FSH, LH, testosterone and DHEA-S were determined by ELISA (DRG Instruments GmbH, Marburg, Germany) with a lower limit of sensitivity.

Statistical analysis.

All statistical analyzes were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). The data were expressed as a frequency and mean with standard deviation. Pearson’s correlation coefficient (r) was used to determine the strength of the relationship between the two continuous variables.

Results.

The study included 55 women with PCOS, and mean age was 21.36 ± 4.29 years with a range of 18-39 years. The mean and standard deviation of BMI in PCOS women was 20.96 ± 2.50 , while the mean values of the LH level and the LH/FSH ratio were quite high (LH= 8.17 ± 9.66 , LH/FSH ratio= 2.86 ± 2.74 , respectively). On the other hand, FSH values did not show any significant increase (FSH= 4.16 ± 2.97) (Table 1).

Table 1. Distribution according to age, BMI and hormonal parameters.

Variables	PCOS (n=55)	
	N	%
Age	21.36±4.29	
Weight	58.82±7.54	
Height	167.53±4.98	
BMI	20.96±2.50	
Hormonal status		
LH	8.17±9.66	
FSH	4.16±2.97	
LH/FSH ratio	2.86±2.74	

Most of the women with PCOS had hirsutism and acne (32.73% and 48.18%) and significantly higher values of testosterone and DHEAS (18.18% and 34.55%) (Table 2).

Table 2. Percentage of hirsutism, acne, testosterone, and DHEA-S in women with PCOS.

Variables	PCOS (n=55)	
	N	%
Hirsutism	36	32.73
Acne	53	48.18
Testosterone	10	18.18
DHEA-S	19	34.55

Figure 1 shows a positive correlation between PCOS and LH/FSH ratio, which means that women with PCOS had higher LH/FSH ratio (r=0.3).

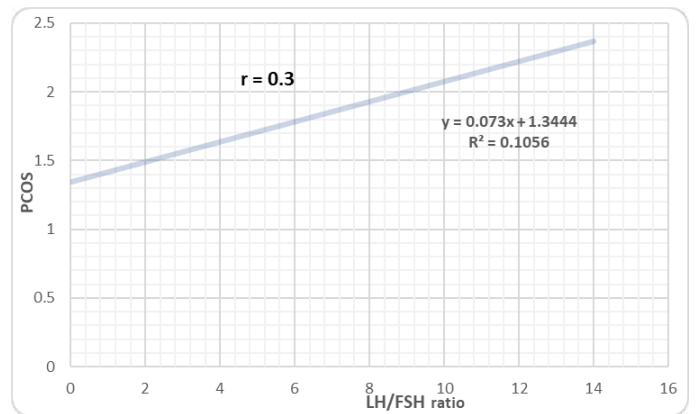


Figure 1. The correlation between PCOS and LH/FSH ratio.

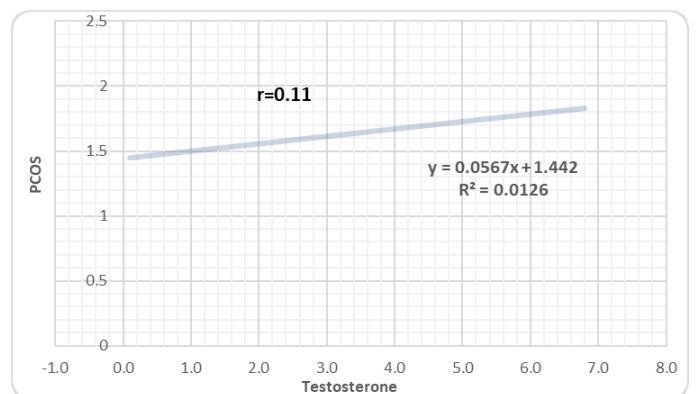


Figure 2. The correlation between PCOS and testosterone levels.

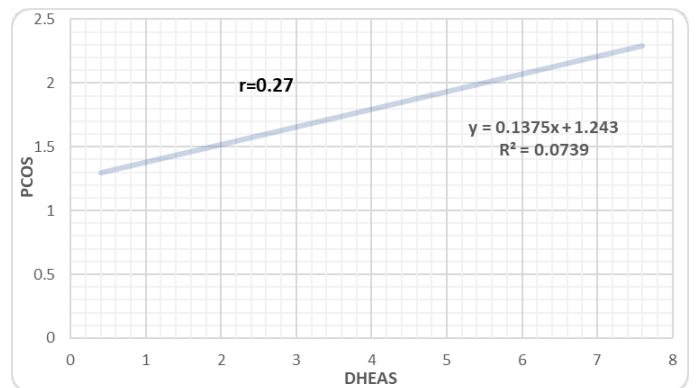


Figure 3. The correlation between PCOS and DHEA-S levels.

Additionally, it is also seen that women with PCOS tend to have higher testosterone values (r= 0.11) (Figure 2).

Moreover, women with PCOS had higher DHEA-S levels, indicating a positive correlation between PCOS and DHEA-S (r=0.27) (Figure 3).

Discussion.

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women which manifests with multiple symptoms and affects women throughout life [3]. The current study assessed joint effects of BMI, hirsutism, acne, and hormonal status in women with PCOS.

Our study shows that PCOS has no influence on BMI, even though other studies illustrate that obesity and PCOS are correlative in their pathogenesis [20]. There are several different

types of acne, and four factors are known to contribute to the development of acne lesions: the plugging of follicles by debris, inflammation in the skin, increased production of sebum and presence of bacteria *Propionibacterium acnes* [20,21]. Furthermore, hirsutism affects women with PCOS, as indicator of increased androgens [22]. We have displayed that over 30% of women with PCOS have hirsutism and acne. These women with acne may represent a particular subpopulation of women with the polycystic ovary syndrome. The association of acne with PCOS has also been reported by other studies [23,24]. Contrary to our study, Ozdemir S et al, has shown that acne is not associated with PCOS women [25].

Abnormality of the hypothalamic-pituitary-ovarian or adrenal axis has been imposed in the pathophysiology of polycystic ovary disease. Ovarian estrogen is responsible for causing an abnormal feedback mechanism that induced an increase in LH release. The normal gonadotrophin axis is disturbed in PCOS women; therefore, LH levels increase, and FSH levels decrease, leading to a reversal of LH/FSH ratio [26]. Usually, in healthy women, the ratio of LH/FSH lies between 1 and 2. In polycystic ovary disease women, this ratio becomes reversed, and it might reach as high as 2 or 3 [11,27]. We found the same results in our study regarding LH, FSH values and LH/FSH ratio in women with PCOS, which are consistent with the findings of the study by Lal L et al. [28]. Moreover, Alnakash AH et al, reported correlation and association between LH/FSH ratio and PCOS [29]. As a result of the increased LH/FSH ratio, ovulation does not occur in patients with polycystic ovary disease. The mainstay of PCOS treatment includes lifestyle modifications and medications including oral contraceptives, antiandrogen therapy and anti-insulin medications such as metformin, followed by ovulation induction with clomiphene citrate [11].

The major circulating steroids generally classified as androgens include dehydroepiandrosterone sulphate (DHEA-S), dehydroepiandrosterone (DHEA), androstenedione (A), testosterone (T), and dihydrotestosterone. DHEA or DHEA-S can also serve as a pre-hormone for the formation of androgens, and may be very important during postmenopausal years [30]. At present, testosterone is the most common measurement in routine clinical practice for the investigation of female hyperandrogenism [31]. Furthermore, in the present study we observed statistically significant positive correlations between PCOS with testosterone and DHEA-S, and these results are consistent with the study done by Münzker J et al. [31]. Overall, we found elevated DHEA-S levels which is in line with previous studies showing that serum DHEA-S is increased in 20% to 30% of women with PCOS [32,33].

Conclusion.

PCOS is not only a reproductive pathology, but also a systemic condition and its etiopathogenesis is still not completely understood. Acne and hirsutism are more common in women with PCOS. The data suggest that the PCOS is in correlation with increased LH/FSH ratio. Women with PCOS are associated with higher concentrations of testosterone and DHEA-S. Large studies are needed to confirm our findings.

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Competing Interests.

The authors declare that they have no competing interests.

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