GEORGIAN MEDICAL NEWS

ISSN 1512-0112

N0 10 (331) Октябрь 2022

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

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.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

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 ВИНИТИ 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.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

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. Корректура авторам не высылается, 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 compu-ter-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 საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ 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 შეღებვის 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 ფჩხილებში 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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Содержание:

GEORGIAN MEDICAL NEWS
No 10 (331) 2022

HOMOCYSTEINE LEVEL IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME (PCOS) WITH AND WITHOUT INSULIN RESISTANCE

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Abstract.

Introduction: Until recent period, hyperinsulinemia and hyperandrogenism were thought to be involved in the pathogenesis of polycystic ovary syndrome (PCOS), however, in recent years several studies reported that hyperhomocysteinemia, which may be associated with insulin resistance, plays important role in the pathogenesis of PCOS. Therefore, hyperhomocysteinemia (HHcy) can be considered as one of the newly identified characteristics of PCOS.

Aim of the study: The aim of the study was to evaluate homocysteine (Hcy) levels in patients with PCOS with and without insulin resistance.

Materials and methods: The study was conducted in 59 patients with PCOS aged 13-35 (mean age 24.5 ± 3.5). Patients were divided into 2 groups: Group I - 38 patients with PCOS and insulin resistance, Group II - 21 patients with PCOS without insulin resistance. PCOS patients as well were divided into 3 subgroups according to homocysteine values: low - ≤ 6.09 μmol/l, moderate - 6.10-

9.33 μmol/l, high > 9.34 μmol/l).

Results: In patients with PCOS and insulin resistance were established a significant increase in homocysteine levels, HOMA-IR and BMI indicators compared to those patients with PCOS without insulin resistance. In the group of patients with PCOS with insulin resistance homocysteine level with increased and high normal level of homocysteine (high Hcy subgroup, > 9.34 μmol/l) were significantly more common (84.2%) compared to patients without insulin resistance (52%).

Conclusion: Homocysteine level is significantly elevated in patients with PCOS, and insulin resistance compared to patients without insulin resistance. In the management of patients with PCOS, along with correction of insulin resistance, control and correction of homocysteine level should be considered, which will improve their reproductive outcome.

Key words. PCOS, homocysteine, hyperhomocysteinemia, insulin resistance, RPL, infertility.

Introduction.

Endocrine disorders are one of the leading causes of infertility in women. According to different studies, rate of polycystic ovary syndrome (PCOS) in female infertility of endocrine genesis is 5-15% [1,2]. Clinically it is manifested by anovulation, oligo-amenorrhea, infertility, hirsutism, acne, and obesity [3]. 5-10% of clinical manifestations depend on race, ethnicity, environmental factors, and phenotype [2].

PCOS is not manifested only by reproductive system disorders. It is associated with obesity, insulin resistance, dyslipidemia, and metabolic syndrome, leading to future health disorders such as cardiovascular system diseases and type 2 diabetes [4,5].

Achieving pregnancy is not enough to perform of fertility. It is very important to maintain this pregnancy, bring it to the term and give live birth.

It was determined that PCOS is one of the most important risk factors not only for infertility but also for pregnancy loss. In particular, in women with PCOS the risk of pregnancy loss, according to various studies varies between 25-73% [6-8].

At present, diagnosis of PCOS is based on the diagnostic criteria adopted at the 2003 Rotterdam Consensus (The Rotterdam ESHRE ASRM–Sponsored PCOS Concesus. Workshop 2003), according to which diagnosis of PCOS is made if at least two of the three criteria are positive [9-12]. These criteria are oligo- amenorrhea and/or chronic anovulation; clinically and/ or biochemically confirmed hyperandrogenemia; multifollicular ovaries (≥ 12 follicles with 2-9 mm diameter, or one or both ovary volume >10 m^3).

According to this Consensus, thyroid dysfunction, hyperprolactinemia, androgen–producing tumors, adrenal hyperplasia, and Cushing syndrome should be excluded.

In recent years, along with hyperandrogenism and hyperinsulinemia in the pathogenesis of PCOS, the probable role of hyperhomocysteinemia and its association with insulin resistance has been discussed. Literary data in this regard are scarce and contradictory [2,6-8].

Homocysteine is a non–protein α-amino acid and homologous to amino acid cysteine. It is formed from amino acid methionine, which is a building block of protein in the body and is excreted in the urine after metabolism [9]. Its metabolic pathway covers remethylation to methionine or trans sulfation to cystathionine. The first pathway of metabolism needs folate and B12 vitamin, the second pathway requires pyridoxal 5′-phosphate. Blocking of remethylation process results in increase in the level of homocysteine in the plasma due to folate and B12 vitamin, as well as methyl tetrahydrofolate reductase (MTHFR) enzyme deficiencies [2].

It is known that homocysteine and insulin induce each other by inhibiting hepatic cystathionine β–synthase (CBS). This results in hyperhomocysteinemia followed by development of insulin resistance and compensatory hyperinsulinemia. This may impair activity of MTHFR or CBS enzymes, leading to elevation of homocysteine levels in plasma [2,13-16].

According to the case–control studies conducted in 2013 by Sachan Rekha and in 2018 by Pranita Maharjan with co-authors, blood serum homocysteine levels were significantly high in both, women with PCOS who had excess weight, as well as with a normal body mass and were in positive correlation with HOMA–IR [2]. Some authors believe that high level of homocysteine in women with PCOS are not related to the degree of obesity, insulin resistance status, and androgen level.

However, metformin therapy does not reduce homocysteine level in patients with PCOS [3].

It is established that several factors affect the level of homocysteine in blood serum. These are: age, gender, tobacco use, physical activity, chronic inflammatory process, nutrition (deficiency of folic acid, vitamin B6 and B12 in food), genetic disorders (MTHFR and CBS gene mutations), hypothyroidism, kidney failure, some medications (atrovastatin, fenofibrate, methotrexate, nicotinic acid). Race and ethnicity should be taken into account.

Hyperhomocysteinemia is associated with early pregnancy loss, in particular, hyperhomocysteinemia increases hypercoagulability status of pregnancy and likelihood of thrombosis in the maternal and fetal blood circulation system. Hyperhomocysteinemia impaires implantation through interfering with endometrial blood flow. As a result, this leads to adverse pregnancy outcomes, including development of pregnancy loss in the preimplantation period [9,17].

At late terms of pregnancy hyperhomocysteinemia contributes increase the rates of gestational diabetes, pregnancy hypertension, preeclampsia (PE), preterm placental abruption, preterm labor (PTL), intrauterine growth restriction (IUGR), Caesarean section. In addition, hyperhomocysteinemia is associated with fetal neural tube defects [7,9,18].

In recent years, there is a great interest in the study of homocysteine level in the blood and regulation of elevated level in the complex management of PCOS. Some researchers consider homocysteine to be a diagnostic marker for PCOS, since in their studies, elevated homocysteine values correlate with high BMI, reduced ovulation rate, and lowered total estradiol levels in serum in women with PCOS [3,12,19,20,]. However, some studies do not confirm the importance of homocysteine level in the diagnosis of PCOS and in evaluating the effectiveness of treatment.

Interesting data were obtained when dividing homocysteine levels into groups, where homocysteine values are divided into 3 levels: lower triplet -HCY ≤ 6.09 μmol/l, middle triplet - HCY 6.10 - 9.33 μmol/l, upper triplet HCY > 9,34 μmol/l [21]. Authors considered that it is important not only to have homocysteine rates higher than normal, but also to have high values within the normal range [21].

Heterogeneity of normal homocysteine levels remains a subject of debate in the literature, as the threshold for homocysteine elevation that can be considered diagnostically reliable has not yet been established. It is not excluded that there is a difference in the threshold values of the norm in different ethnic groups. It should be noted that homocysteine level in PCOS cases in Georgian patients were analyzed for the first time in our study.

Studies in this direction have only been started in recent years and are therefore few. The issue requires further study and discussion. Therefore, conducting such researches and accumulating data in this direction is appropriate and relevant.

Aim of the study.

The aim of the study was to evaluate homocysteine levels in patients with PCOS with and without insulin resistance.

Materials and methods.

Prospective observational research design was selected for the study. This work is based on open label research, foundation of which is observation of groups of patients.

Consent of the Ethical Committee of the Center for Reproductive Medicine "Universe" was obtained for conducting the study.

Before inclusion in the study all participants were informed in advance, the essence and purpose of the study were explained to them. Written consent to participate in the study was obtained.

Inclusion criteria: Diagnosis of PCOS according to the Rotterdam Consensus criteria ; Age ≤ 35 years, ≥ 2 years from menarche. **Exclusion criteria:** Patients with thyroid dysfunction, hyperprolactinemia, androgen – producing tumors, Cushing syndrome, history of surgical intervention on reproductive organs; Less than 6 months has passed since hormone therapy before inclusion in the study, age > 36 years; < 2 years from menarche.

Study group included 59 Georgian women with PCOS aged 13-35 (mean age 24.5 ± 3.5). Before inclusion in the study all patients underwent assessment of personal and family history, menstrual function, clinical and instrumental - laboratory examination.

Personal history was collected: age, age of menarche, nature of menstrual function, age of menstrual cycle disorder, reproductive function, fertility problems, intensity of manifestation of dermatopathies and age of their manifestation.

Body mass index (BMI) was determined for all patients during their visit to clinic using the formula by G. Brey (1978) : I=m/ h2, where **I** is body mass index, **m** – body mass in kilograms and **h** - body height in meters.

In order to determine peculiarities of body adipose tissue distribution the index of ratio of waist and hip circumferences (in centimeters) was determined.

All patients were assessed for dermatopathies: hirsutism was assessed using Ferriman - Galwey's modified hirsutism grading scale (mFG). Acne was assessed according to 3 categories (mild, moderate, and severe), striae (white and colored - pink, red or dark burgundy). Presence of hyperpigmentation (acanthosis nigricans) was determined.

All participants underwent an ultrasound examination of small pelvic organs on the 2^{nd}-3^{rd} day of the menstrual cycle. Ultrasound was performed with VOLUSON E10 (produced by General Electric, USA).

All participants underwent hormonal examination on the 2^{nd}–3^{rd} day of menstrual cycle. The levels of following hormones in blood serum were determined: AMH, FSH, LH, T, FT, SHBG, Insulin and HOMA-IR. To determine exclusion criteria: TSH, FT4, anti - TPO, anti - TG, PRL, 17 OHP, DHEA-S, cortisol by immunoenzymatic method (ELISA, Beckman Coulter, USA).

Serum homocysteine levels were measured using closed system immunoenzymatic analyzer Tosoh Bioscience, Japan according to the manufacturer's protocol. Reference values are 5-15 μmol/l.

According to insulin resistance indicators 59 patients of the study group were divided into 2 groups: Group I - 38 patients

with PCOS and insulin resistance, Group II - 21 patients with PCOS without insulin resistance.

According to homocysteine values, patients were divided into 3 subgroups : low - ≤6,09 μmol/l, moderate - 6,10 - 9,33 μmol/l, high > 9,34 μmol/l.

Statistical analysis.

The obtained data were processed using statistical analysis programs SPSS 24.0 (Statistical Package for Social Sciences, version 24) using independent samples T test.

Results.

According to the data of our study 35 patients (92.1%) in group I had menstrual cycle disorders in the form of oligomenorrhea and 15 patients in group II (71%) (P< 0,05). Moderate and severe acne was detected in 30 patients (79%) in group I and 15 patients in group II (71%) (P> 0.05). Moderate and severe hirsutism was observed in 34 patients (89.5%) in group I and 17 patients in group II (81%) (P > 0.05). Manifestations of severe and moderate hirsutism and acne were not significantly different in patients with PCOS with and without insulin resistance. Acanthosis nigricans was observed only in PCOS patients with insulin resistance (11 patients, 28,9%).

In group I increased BMI were significantly more frequent (9 patients, 22%) compared to group II (1 patient, 5%) (P < 0.05). Abdominal distribution of body fat (waist–to–hip circumference >0.8) in group I was observed in 35 patients (92%) both in case of overweight and normal BMI. In group II abdominal distribution of adipose tissue was detected in 6 patients (29%) (P < 0.001).

In the group of women with insulin resistance (group I) out of 35 sexually active patients, 9 patients (25.7%) had primary infertility, 3 patients were sexually inactive, but had an anovulatory menstrual cycle. In group II, primary infertility occurred in 8 out of 20 sexually active patients (40%), 1 patient was sexually inactive but had an anovulatory menstrual cycle (P>0.05).

Recurrent pregnancy loss (RPL) occurred in 29 out of 35 patients (82.9%) in group I and in 12 out of 20 patients in group II (60%) (P>0.05).

Table 1 shows results of comparative analysis of two groups, which were compared according to the mean values of 11 variables (different hormone secretion levels). The t–test showed that comparable groups (groups I and II) did not significantly differ from each other in terms of most of the analyzed variables. Exceptions from the variables are HOMA-IR (mean HOMA-IR 3.88 in the group with insulin resistance and 1.2 in the group without insulin resistance) and IRI (group I -mean IRI-14,8, group II- 4,54) (P<0.001), whose mean values in comparable groups differ sharply and significantly from each other. Patients were divided into groups based on these data.

As a result of our study the average values of homocysteine were significantly higher in group I compared to group II (group I mean Hcy-14,6 mg/l, group II - 9,2 mg/l) (P<0.001).

Compared to the reference levels of homocysteine, an increased rate was detected in 4 patients (11%) in group I, and in none of the patients in group II (0%).

In patients with PCOS and insulin resistance, revealed a significant increase in the rate of elevated homocysteine, HOMA-IR and BMI compared to patients with PCOS who did not have insulin resistance.

Results of our study, which were considered after dividing the homocysteine levels into 3 subgroups (low, moderate, high) turned out to be very interesting. It was determined that in patients with insulin resistance (Gr. I) increased and high normal levels of homocysteine were detected in 84% of cases (32 patients), moderate - in 11% (4 patients), low - in 5% (2 patients). In patients without insulin resistance (Gr.II), these indicators were respectively: high - in 52% (11 patients) (P<0.05), moderate - in 38% (8 patients) (P<0.05), low - in 10% (2 patients) (P>0.05) (Figure 1).

Discussion.

Until recent period, hyperinsulinemia and hyperandrogenism were considered to be involved in the pathogenesis of PCOS, however, in recent years several studies reported that hyperhomocysteinemia, which may be associated with insulin resistance, plays important role in the pathogenesis of PCOS [2,6-8].

As a result of our study, it was determined that average level of homocysteine was found to be significantly higher in PCOS patients with insulin resistance compared to patients who did not have insulin resistance, which conforms with the data in the literature [2,17,21-25]. However, number of studies have not established a relationship between homocysteine level and insulin resistance in patients with PCOS [26-30].

Table 1. *Comparative analysis of variables in PCOS women with insulin resistance (group I) and without insulin resistance (group II).*

Group		Age	BMI	IRI (MU/ml)	HOMA-IR	Testosterone (ng/ml)	Free T (nmol/l)	SHB G	LH/FSH ratio	AMH (pmol/l)	Ov/V ol	AF C	Hcy (μmol/l)
1	N of patients	38	38	30	38	32	30	30	32	30	30	30	38
	Mean	2 ,53	24,18	14,355	3,369	0,81	3,713	43,32	2,531	12,06	14,3	33,78	12,74
	Std. Deviation	2,938	3,935	2,0601	0,8167	0,271	1,6192	24,361	0,2989	4,391	2,01	5,29	2,792
2	N of patients	21	21	16	21	15	15	15	16	15	15	15	21
	Mean	5,33	21,4	4,363	1,21	0,82	3,387	49,39	2,563	11,76	13,48	30,73	9,21
	Std. Deviation	2,153	3,123	1,6701	0,4989	0,221	0,7963	20,741	0,35	5,653	2,45	5,788	2,336
	P valu e	0,274	0,007	<,001	<,001	0,886	0,466	0,414	0,749	0,845	0,238	0,085	<,001

Values are expressed as the mean ± SD.

Significant difference between groups (p < 0.05).

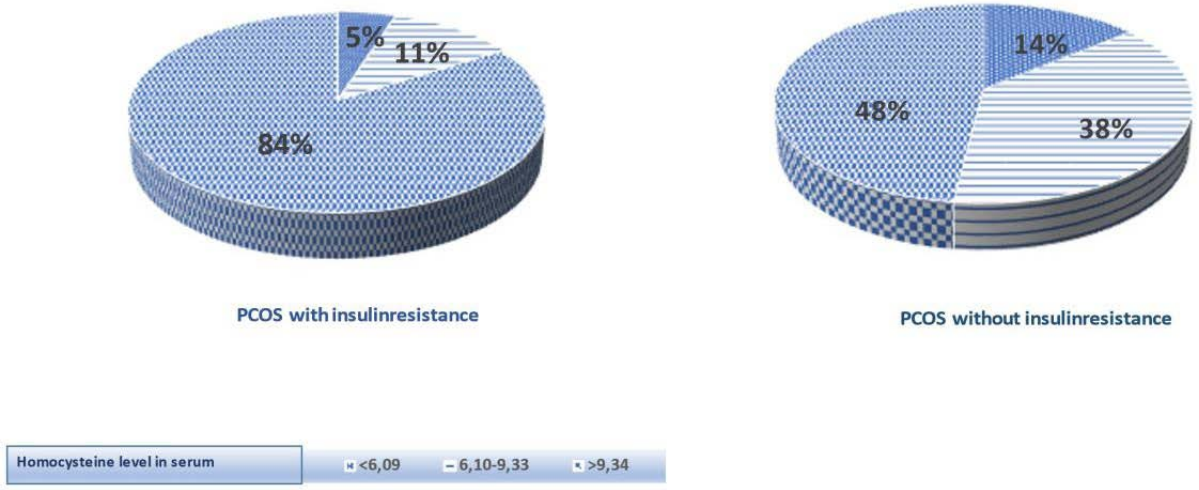

Figure.1. *Distribution of patients according to homocysteine levels in patients with PCOS and insulin resistance and PCOS without insulin resistance.*

In the literature, there are heterogeneous data on association between BMI and homocysteine. In our study patients with PCOS and insulin resistance had significantly higher homocysteine level, BMI and HOMA–IR compared to the group of patients with PSOC without insulin resistance. Our data conform with the data of the study conducted by Guzelmeric K, Alkan et al. [27]. However, a study by Rojeen Rasheed Suleiman, Al-Gareeb et al. found no significant difference between homocysteine levels in cases of normal and high BMI in patients with PCOS [22,31].

Some believe that high levels of homocysteine in women with PCOS are not related to the degree of obesity, insulin resistance status, and androgen levels [6]. Analysis of the results of our study showed that in the subgroup of PCOS patients with increased and high normal levels of homocysteine, significantly higher rate of increase in BMI was observed in the group of patients with insulin resistance compared to the group of patients without insulin resistance.

No papers published have compared menstrual cycle disorders, dermatopathies (hirsutism, acne, acanthosis nigricans), HOMA-IR, IRI and homocysteine in PCOS patients with and without insulin resistance. These data are compared only with the control group, which consisted of healthy women. According to the data of our study clinical and biochemical indicators of hyperandrogenemia were not significantly different in PCOS patients with and without insulin resistance.

To date there are no established normal threshold values for homocysteine, which may be affected by ethnicity, socio-economic status of the country, and consumption of fortified foods in some countries.

Since homocysteine values are characterized by population differences and our study was conducted for the first time among Georgian women, for which there are no data on the threshold values of normal homocysteine values, our focus on the values of normal homocysteine levels was more important than considering of groups according to hyperhomocysteinemia. Results of our study, which were considered after dividing the homocysteine levels into 3 subgroups turned out to be very interesting. It was determined that increased and high normal levels of homocysteine in patients with insulin resistance were significantly more frequently observed in group I compared to group II. This indicates that, as Hui Chang and co–authors discuss in their paper [21], when considering homocysteine levels in the pathogenesis of PCOS not only increased than normal levels of homocysteine, but also elevated levels within the normal range may be important.

Thus, study of homocysteine level in patients with PCOS is of great importance. At the same time, it is important not to discuss absolute hyperhomocysteinemia in this direction, considering that the homocysteine indicators in different ethnic groups are not uniform, but high levels detected within the norm of homocysteine should be paid attention to and taken into account in the management of PCOS.

It is especially important to study homocysteine levels in patients with insulin resistance. According to current literature, metformin therapy do not provide correction of homocysteine [3], therefore, correction of homocysteine should be given special attention.

Some authors believe that taking into account results of their studies, elevated serum homocysteine level can be considered as PCOS biomarker [31]. Our study results indicates that level of homocysteine can be considered as a characteristic of PCOS.

Heterogeneity of data from studies may be due to the fact that homocysteine levels vary by age, population, diet, and number of other factors, and therefore no threshold values have been established. It is important to conduct population studies to determine the threshold values of normal range of homocysteine, including Georgian population.

Conclusion.

Homocysteine level is significantly elevated in patients with PCOS, and insulin resistance compared to patients without insulin resistance. In the management of patients with PCOS, along with correction of insulin resistance, control and correction of homocysteine level should be considered, which will improve their reproductive outcome.

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აბსტრაქტი

შესავალი: ბოლო პერიოდამდე პოლიცისტური საკვერცხეების სინდრომის (პსს) პათოგენეზში მოიაზრებდნენ ჰიპერინსულინემიას და ჰიპერანდროგენიას, თუმცა ბოლო წლებში გაჩნდა შრომები იმის შესახებ , რომ პოლიცისტური საკვერცხეების სინდრომის პათოგენეზში მნიშვნელოვან როლს ასრულებს ჰიპერჰომოცისტეინემია, რომელიც შეიძლება ასოცირებდეს ინსულინრეზისტენტობასთან. ამდენად, ჰიპერჰომოცისტეინემია (ჰჰც) შეიძლება იყოს განხილული, როგორც პსს-ის ერთ-ერთი ახლადგამოვლენილი მახასიათებელი.

კვლევის მიზანი: კვლევის მიზანს წარმოადგენდა ჰომოცისტეინის (ჰც) მაჩვენებლების შეფასება პსს-ის მქონე პაციენტებში ინსულინრეზისტენტობით და

ინსულინრეზისტენტობის გარეშე.

მასალა და მეთოდები: კვლევა ჩატარდა 13-35 წლის ასაკის 59 პაციენტში პსს-ით (საშუალო ასაკი 24.5±3.5). გამოკვლეული პაციენტები დაიყო 2 ჯგუფად: I ჯგუფი - 38 პაციენტი პსს-ით და ინსულინრეზისტენტობით, II ჯგუფი - 21 პაციენტი პსს-ით ინსულინრეზისტენტობის გარეშე. პაციენტები დაყოფილი იყვნენ 3 ქვეჯგუფად ჰომოცისტეინის მაჩვენებლების მიხედვით: დაბალი - ≤6,09 μmol/l, საშუალო - 6,10 - 9,33 μmol/l, მაღალი > 9,34 μmol/l).

შედეგები: კვლევის შედეგად პაციენტებში პსს-ით და ინსულინრეზისტენტობით მივიღეთ ჰომოცისტეინის, ჰომა- ინდექსის და სმი-ს მაჩვენებლების სარწმუნო მომატება პსს-ის მქონე იმ პაციენტებთან შედარებით, რომელთაც ინსულინრეზისტენტობა არ აღენიშნებოდათ. დადგინდა, რომ პსს-ს მქონე პაციენტების ჯგუფში

ინსულინრეზისტენტობით სარწმუნოდ ხშირად ვლინდება (84,2%) ჰომოცისტეინის მომატებული და ნორმის მაღალი მაჩვენებლები (მაღალი ჰც ქვეჯგუფი, >9.34 μmol/l) იმ პაციენტებთან შედარებით, რომელთაც ინსულინრეზისტენტობა არ აღენიშნებოდათ (52%).

დასკვნა: პაციენტებში პსს-ით და ინსულინრეზისტენტობით ჰომოცისტეინის დონე სარწმუნოდ მომატებულია იმ პაციენტებთან შედარებით, რომელთაც

ინსულინრეზისტენტობა არ აღენიშნებათ . პსს-ს მქონე პაციენტების მენეჯმენტში გათვალისწინებული უნდა იყოს ინსულინრეზისტენტობის კორექციასთან ერთად ჰომოცისტეინის დონის კონტროლი და კორექცია, რაც გააუმჯობესებს მათ რეპროდუქციულ გამოსავალს.

Абстракт

Введение: Считается, что гиперинсулинемия и гиперандрогения участвуют в патогенезе синдрома поликистозных яичников (СПКЯ), однако в последние годы появились данные об участии гипергомоцистеинемии в патогенезе СПКЯ, которая может быть связана с инсулинрезистентностью. Таким образом, гипергомоцистеинемию (ГГЦ) можно рассматривать как одну из недавно выявленных характеристик СПКЯ.

Цель исследования: Определить уровни гомоцистеина (Нсу) у пациенток с СПКЯ с резистентностью к инсулину и без нее.

Материалы и методы: Исследование проведено у 59 пациенток с СПКЯ в возрасте от 13 до 35 лет (средний возраст 24,5 ± 3,5 года). Пациентки были разделены на 2 группы: I группа - 38 пациенток с СПКЯ и инсулинорезистентностью, II группа - 21 пациенка с СПКЯ без инсулинорезистентности. Пациентки с СПКЯ также были разделены на 3 подгруппы по **уровню гомоцистеина:** низкий - ≤ 6,09 мкмоль/л, средний - 6,10-9,33 мкмоль/л, высокий > 9,34 мкмоль/л).

Резуьтаты: У пациенток с СПКЯ и инсулинорезистентностью выявлено достоверное повышение уровня гомоцистеина, показателей HOMA-IR и ИМТ по сравнению с таковыми у пациенток с СПКЯ без инсулинорезистентности. В группе пациенток с СПКЯ с инсулинорезистентностью уровни гомоцистеина с повышенным и высоким нормальным уровнем гомоцистеина (подгруппа с высоким Нсу > 9,34 мкмоль/л) встречались достоверно чаще (84,2%) по сравнению с пациентками без инсулинорезистентности (52%).

Выводы: Уровень гомоцистеина достоверно повышен у пациенток с СПКЯ и инсулинорезистентностью по сравнению с пациентками без инсулинорезистентности. При ведении больных с СПКЯ наряду с лечением инсулинрезистентности следует корректироватъ уровень гомоцистеина, что улучшит их репродуктивный исход.