

To the chairman of the scientific jury:
Prof. Dr. Emil G. Kovachev, MD, PhD, DSc, St. Marina University Hospital, Varna
Medical University – Faculty of Medicine, Varna,
Appointed by order No. R-109-282 of 30.07.2026 of the Rector of MU - city of Varna,
Based on a decision under protocol No. 1/12.08.2026 of
Department Council at the Department of Pediatrics and report with entry No. 102-1673/08.07.2026.
From the Dean of the Faculty of Medicine of the Medical University of Varna "Prof. Dr. Paraskev
Stoyanov" - Varna

REVIEW

by Assoc. Prof. Dr. Nartsis Nisim Kaleva-Hodzheva, MD, PhD,

specialist in pediatrics and pediatric endocrinology,
until the end of 2021, Head of the Endocrinology Unit at the Pediatrics Clinic of St. George
University Hospital - Plovdiv and Associate Professor at the Department of Pediatrics and
Medical Genetics, Faculty of Medicine, Medical University, Plovdiv

of a dissertation for the award of the educational and scientific degree 'doctor',

Professional field 7.1 Medicine, Field of higher education

7. Health and Sports, Doctoral Program "Pediatrics"

Author: **Dr. VILHELM RUSLANOV MLADENOV**

Form of doctoral studies: **full-** time

Department : "Pediatrics", Faculty of Medicine at MU-Varna

Topic: "**POLYCYSTIC OVARY SYNDROME IN ADOLESCENCE – CONTEMPORARY
ASPECTS AND DIRECTIONS FOR DIAGNOSIS**"

Scientific supervisor: PROFESSOR DR. VIOLETA MIHOVA IOTOVA, MD, PHD, DSC.

1. GENERAL OVERVIEW OF THE PROCEDURE AND THE DOCTORAL STUDENT

The presented set of materials on paper and electronic media is in accordance with the Regulations of the Medical University of Varna for the acquisition of the educational and scientific degree "DOCTOR" and the scientific degree "DOCTOR OF SCIENCES" at the Faculty of Medicine at the Medical University of Varna and includes the following documents:

1. Dissertation – original Word and PDF format, as well as on paper.
2. Abstract – original Word and PDF format, as well as on paper.

3. Application to the Rector for the opening of a defense procedure.
4. Creative CV in European format with the signature of the doctoral student.
5. Diploma for the educational and qualification degree "Master" with appendix.
6. List of publications and scientific papers on the topic with the signature of the doctoral student.
7. A copy of the publications related to the topic of the dissertation.
8. Declaration of originality and declaration of accuracy of information.
9. Order for enrollment in doctoral studies.
10. Order for expulsion from doctoral studies with the right to defend.
11. Minutes from the Constitutional Court with a positive decision on readiness for defense.
12. Exam transcripts - doctoral minimum in the specialty and for a foreign language
13. Declaration of registration of the profile in scientific databases.
14. Similarity certificate from the similarity checking program from the Publishing Department.
15. Proof of an up-to-date profile with a full list of scientific publications on Google Scholar and ORCID, issued by the Library of the Bulgarian University - Varna.
16. Application to the Rector for the opening of a defense procedure.

The submitted documents meet the requirements of the Medical University - Faculty of Medicine - Varna.

2. BIOGRAPHICAL DATA AND PROCEDURAL REQUIREMENTS:

Dr. Vilhelm Ruslanov Mladenov was born on February 6, 1970 in Varna. He graduated from the First English Language School in Varna in 1989 and from the Medical University "Prof. Dr. Paraskev Stoyanov" in Varna in 1995. In 2002, he specialized in pediatrics, and in 2007, in pediatric endocrinology and metabolic diseases.

Over the years, he has had the opportunity to participate in international and national training courses, has participated in congresses and symposiums in the country and abroad. Since 2017, he has been an assistant at the Department of Pediatrics at MU-Varna, actively participating in the training of students, interns and residents at the department - both in Bulgarian and English. He has worked successively at the RHIF - Varna as an expert, from 2003 to 2009 at the "St. Anna" Hospital - Varna as a pediatrician, and since 2009 at the "St. Marina" University Hospital in the First Pediatric Clinic as a pediatrician and pediatric endocrinologist. Dr. Wilhelm Mladenov has full potential to develop successfully as a pediatrician and pediatric endocrinologist both in practical and scientific directions.

The emphasized clinical and scientific interests of the doctoral student are in the field of DSD and polycystic ovary syndrome. He has attended the ESPE winter school - Varna - 2006, ISPAD scientific school - Hvidovre - Denmark - 2007, specialized as clinical fellow in the field of DSD in Ghent - Belgium - 2011 and attended numerous - 8 - postgraduate courses of ISPAD/VAPES. He has been a lecturer at the national conference on pediatric endocrinology with international participation in Timisoara/Romania in 2013 and at the 7th conference in 2023 in Pomorie/Bulgaria. He is a member of several scientific societies and organizations: Bulgarian Medical Union, Bulgarian National Society of Pediatric Endocrinology, Bulgarian

Endocrinological Society, ESPE, ISPAD, Varna Society of Pediatric Endocrinology, Bulgarian Society of Human Genetics and Genomics.

He has over 30 publications in Bulgarian and international journals with over 200 citations. He is fluent in written and spoken English.

Dr. Vilhelm Mladenov has presented a dissertation containing main sections according to the requirements, namely: Introduction; Literature review; Background, aim and objectives; Design, participants and methods of the study; Results; Discussion; Conclusions; Contributions; Conclusion; Own publications, communications and participations related to the dissertation; Appendices; Bibliography.

An abstract is also presented, as well as the publications cited on the topic. The dissertation contains a total of 177 pages, illustrated with 25 tables and 16 figures. The bibliography contains 180 literary sources, of which 4 are in Cyrillic and 176 in Latin.

The publication activity and participation in scientific forums are sufficient according to the requirements of the Regulations of the Medical University - Varna for defense. In connection with the dissertation, there are four scientific publications of which Dr. Mladenov is the first author and four scientific communications, one of which at the ESPE congress in 2024, of which he is also the first author.

In summary, the structure of the dissertation work and the independent participation of the dissertation candidate in its preparation comply with the procedural requirements.

3. RELEVANCE OF THE TOPIC

The dissertation is dedicated to polycystic ovary syndrome. Although the condition has long been known to clinicians – endocrinologists and gynecologists – it was first described in 1935 by the American gynecologists Stein and Lowenthal, although it is one of the most common endocrine disorders and the most common condition associated with hyperandrogenemia in adolescent and young female age, its etiopathogenesis continues to be incompletely understood. Statistics show a sharp increase in the number of publications related to the syndrome in the last 3 decades, and other specialists, besides described above, are already showing interest in it. The leading pathological symptoms – oligomenorrhea, obesity, clinical and hormonal manifestations of hyperandrogenemia, lead to consequences regarding the quality of life of the patients, impaired fertility, cardiovascular complications and an increased risk of malignant pathology. This increases the palette of specialists forming the multidisciplinary team caring for these patients. It also includes cardiologists, psychiatrists, psychologists, oncologists, laboratory doctors, imaging specialists, etc. The dynamics of the name of the condition - from "Stein- Löwenthal Syndrome ", through "Polycystic Ovarian Syndrome" (PCOS), to the now introduced " Polyendocrine Metabolic Ovarian Syndrome" (PMOS) reflects its growing importance and interest. Despite all of the above, the adolescent age, in which the syndrome actually manifests itself for the first time, remains in the background again. And this is the age in which timely diagnosis and treatment is the correct secondary prevention of later consequences. There are also no categorical diagnostic criteria for a reliable diagnosis of this condition, as well as for differential diagnosis with similar and typical diseases for this age.

In support of all this - the choice of topic by Dr. V. Mladenov fills the void not only in Bulgarian, but also in world science and practice. The high incidence of the disease with its debut in adolescence and the tendency to increase create a need for more precise methods for its early diagnosis and timely and effective interventions to prevent and reduce the health and socio-economic consequences of its complications.

All this suggests that the topic is relevant and that its choice is proof of the professionalism of the dissertation candidate and his scientific supervisor.

4. KNOWING THE PROBLEM

The presented dissertation is written in correct Bulgarian, the review, supported by the own publications, is thorough and motivates the choice of topic. The number of patients and control subgroups covered is sufficient in number after the correctly selected methods of statistical processing. The logic of the conclusions made, corresponding to the goal and tasks and based on a thorough statistical analysis, prove the excellent knowledge of the problem by the dissertationist.

5. RESEARCH METHODOLOGY

The clinical, laboratory and statistical methods presented in the dissertation are appropriate to the goal and objectives and prove the thesis of the dissertation candidate.

6. CHARACTERISTICS AND EVALUATION OF THE DISSERTATION AND CONTRIBUTIONS

The presented dissertation has a total volume of 177 standard typewritten pages, of which 41 pages are a literature review, and the rest are dedicated to examining the goal, objectives, methodologies, results, discussion, conclusions corresponding to the set goals and objectives, contributions, applications and literary sources.

The literature review is purposefully constructed, with emphasis placed on the relevant aspects of the main topic. The individual chapters in the literature review prepare for the selection of emphases of the dissertation work and facilitate the interpretation of own results and the logic of the conclusions drawn. The review presents in detail various new biomarkers described by other authors as reliable or insufficient. The critical view of the dissertation author on the selection of specific biomarkers that became the subject of his study is evident. A special part of the literature review is devoted to the treatment of PCOS, which is not included in the topic of the dissertation work. However, this makes this section of the review useful as an independent educational material.

An interesting transition between the literature review and the original material are the prerequisites for choosing a topic – presented laconically, but sufficiently convincingly and logically. A leading prerequisite is the very scarce studies in our and global scientific literature on PCOS in adolescence, as well as the lack of a modern diagnostic algorithm that includes new biomarkers characterized by higher reliability.

The goal and tasks are precisely formulated and correspond to the title of the dissertation. The results of the own study of the girls divided into three groups are presented visually - verbally, through tables and graphs, with the results of the statistical processing. The tables and graphs are sufficiently clear and accessible for understanding, without unnecessary complication. Sufficient space is allocated to the discussion - again divided according to the tasks set. The results of the own study are compared, in places contrasted with other modern studies. This makes the perception of the information in the dissertation understandable and convincing. Of course, in this study, sufficient space is allocated to proving the consequences of untimely diagnosis, listed further in the conclusions. This part of the dissertation is divided

comprehensively - for each of the 5 own tasks set at the beginning, several conclusions follow for each of them.

7. MATERIAL AND METHODS USED :

The number of patients included in the study is sufficient. The selection of two control subgroups - one of healthy girls of similar age and the other - with idiopathic hyperandrogenemia is adequate in terms of age and anthropometric indicators. This makes the results of the scientific study sufficiently representative and reliable. The clinical, laboratory, imaging, psychological and statistical methods described in detail in the text determine the reliability of the results obtained.

8. CONTRIBUTIONS OF THE DISSERTATION OF DR. VILHELM MLADENOV:

This is the first in the country and one of the few studies worldwide that comprehensively examines Polycystic Ovary Syndrome in adolescent girls. The difficulties in differential diagnosis /DD/ with other diseases characterized by hyperandrogenemia in females are a daily challenge in the practical work of the pediatric endocrinologist. The propaedeutic nature of the review, as well as some of the own results introduce the difficulties of this DD, making this diagnostic task clearer. The main contributions of Dr. V. Mladenov's scientific work are summarized at the end of it: For the first time in our country and for the second time worldwide, the expression of selected micro RNAs is studied. For the first time worldwide, the diagnostic role of miR-320a-5p, miR-103a-5p, miR-15a-5p and miR-194-5p has been proven. Apart from this – as relatively more accessible laboratory indicators, but with sufficient diagnostic value are the studied AMH, Androstenedione and FAI – proven convincingly by statistical methods. All this makes it possible to enrich the diagnostic algorithm for PCOS in girls under 18 years of age with new highly specific and sensitive biomarkers. Of no less value are the detailed clinical, anthropometric, biochemical and classical hormonal characteristics of PCOS, the comorbidity of the condition, presented in the dissertation work and highlighted in the author's conclusion.

9. EVALUATION OF THE PUBLICATIONS AND PERSONAL CONTRIBUTION OF THE DOCTORAL STUDENT

The publications and participations in scientific forums presented are directly related to the topic of the dissertation and in all of them Dr. Wilhelm Mladenov is the lead author. Their number exceeds the requirements of the procedure. Usually the dissertation is the subject of few readers, the abstract – accessible to a slightly larger number of doctors, but publications in scientific journals are the form for distributing a review and own results among a wide audience and this is their great value, beyond their purely scientific qualities.

I have no further comments at this stage.

10. ABSTRACT

The abstract has a total volume of 87 pages and presents all of the author's own results – verbally, with tables and graphs, a detailed discussion, including many of the data from the literature review, through which a logical interpretation of the author's own results and

conclusions is made. I have no additional comments on its content. It adequately corresponds to the dissertation work and even as a standalone reading is informative enough for information and citations.

The abstract meets the requirements of the Medical University - Varna.

11. CONCLUSION

The dissertation contains scientific, scientifically applied and applied results that represent an original contribution to science and meet all the requirements of the Act on the Development of the Academic Staff in the Republic of Bulgaria (ADSRB), the Regulations for the Implementation of the ADSRB and the relevant Regulations of the Medical University - Varna.

The dissertation demonstrates that the doctoral student possesses in-depth theoretical knowledge and professional skills in the scientific specialty of pediatric endocrinology and metabolic diseases, demonstrating qualities and skills for independently conducting scientific research.

Due to the above, I confidently give my positive assessment of the research conducted, presented within the framework of the dissertation, its abstract, achieved results and contributions, and I propose to the esteemed Scientific Jury to award the educational and scientific degree of 'doctor' to Dr. Wilhelm Mladenov .

09/26/2026

Plovdiv

Reviewer: 

Заличено на основание чл. 5, §1, б. „В“ от Регламент (ЕС) 2016/679
--

Assoc. prof. Dr. Nartsis N. Kaleva-Hodzheva, MD, PhD