

STATEMENT

By Assoc. Prof. Chayka Kirilova Petrova, MD, PhD
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Regarding: Dissertation of Dr. Vilhelm Ruslanov Mladenov, full-time doctoral student at the Department of Pediatrics, Medical University of Varna, for the award of the educational and scientific degree “Doctor” (PhD) under the doctoral program “Pediatrics”.

Pursuant to Order No. P-109-282/30.07.2026 of the Rector of the Medical University of Varna and by decision of the Scientific Jury (Minutes No. 1/12.08.2026), I have been appointed to prepare a statement on the dissertation of Dr. Vilhelm Ruslanov Mladenov entitled “Polycystic Ovary Syndrome in Adolescence – Contemporary Aspects and Diagnostic Approaches” for the award of the educational and scientific degree “Doctor” in the professional field 7.1 Medicine, doctoral program “Pediatrics”.

This statement has been prepared in accordance with the requirements of the Act on the Development of the Academic Staff in the Republic of Bulgaria and the Regulations for its implementation at the Medical University – Varna.

Biographical data

Dr. Vilhelm Ruslanov Mladenov was born in 1970 in Varna. He graduated from the First English Language School in his hometown in 1989. He studied medicine at the Medical University of Varna, graduating with a master's degree in 1995. He has worked as an expert at the Regional Health Insurance Fund and as a pediatrician at St. Anna Multiprofile Hospital for Active Treatment, Varna. Since 2009 he has worked as a pediatric endocrinologist at the First Pediatric Clinic of St. Marina University Hospital – Varna, having acquired specialties in Pediatrics (2002) and Pediatric Endocrinology and Metabolic Diseases (2007). He became an assistant professor in 2017 and a full-time doctoral student in 2020 at the Department of Pediatrics, Medical University of Varna.

The scientific interests of Dr. Vilhelm Ruslanov Mladenov lie in the field of rare endocrine diseases, with a focus on DSD. He has completed specializations in Hvidøre, Denmark (ISPAD, 2007), in Ghent, Belgium (2011), at the ESPE Winter School (2006), and 8 postgraduate courses of ISPAD/VAPES. He holds certificates in ultrasound of the endocrine system, DEXA scanning of bone and adipose tissue, insulin pump and CGM therapy, and GCP. He has been a speaker at international conferences: Timișoara, Romania, 2013, and ISPAD/VAPES 2023, Bulgaria. Scientific output: more than 30 publications in Bulgarian and international journals, with more than 200 citations.

1. Assessment of the relevance of the topic

Polycystic ovary syndrome (PCOS) attracts continuous scientific interest owing to the still incompletely elucidated mechanisms of its etiology and pathogenesis. The disease is the most common cause of hyperandrogenism in females, with age-related changes in its clinical presentation and serious long-term reproductive, cardiometabolic and psycho-emotional consequences. The diagnostic methods applied so far in adolescence have proven imperfect because of their overlap with physiological pubertal phenomena. There is a need to validate new diagnostic criteria for adolescence, including new biomarkers highly specific for PCOS. In Bulgaria there is no comprehensive study of PCOS in adolescents, nor a national consensus on its diagnosis and treatment. Studies worldwide are also few. The present dissertation provides a comprehensive study of the clinical and laboratory characteristics and comorbidity

of PCOS in adolescence, together with contemporary diagnostic approaches. In this sense, the study has important scientific and practical significance.

2. Structure of the dissertation

The dissertation is well structured, presenting all main sections on 173 pages, illustrated with 25 tables and 16 figures.

The literature review (40 pp.) demonstrates the author's very good knowledge of the issues studied and his ability to interpret the literature sources. The doctoral candidate has presented, thoroughly and with detailed analysis, the development of knowledge about PCOS. The mechanisms related to its etiology, genetic factors and epigenetics are described in detail. Particular attention is paid to hyperandrogenism as a key pathogenetic factor, including the role of SHBP and the Free Androgen Index (FAI). The clinical manifestations of PCOS and its comorbidity depending on age are presented. The existing diagnostic criteria and their application in adolescence are analyzed. Emphasis is placed on the importance of a number of new diagnostic biomarkers for PCOS (AMH, insulin-like peptide 3 (INS-3), peptin, nesfatin-1, irisin, microRNAs and FAI). Contemporary methods of treating the disease are presented.

Aim and objectives (2 pp.) The dissertation is structured around 5 well-chosen objectives for achieving the precisely and clearly formulated aim.

Design of the author's own research (15 pp.)

The dissertation includes 59 participants up to 18 years of age, 36 of whom have PCOS. The study was conducted as a case-control study over a 2-year period (2021–2023) among girls hospitalized at the First Pediatric Clinic, University Hospital – Varna. Participants were selected using inclusion and exclusion criteria. PCOS was diagnosed according to the criteria of the International Consortium of Paediatric Endocrinology (ICPE). The study was supported by a research project under the “Science” Fund, 2021 – Medical University of Varna.

The collected data were processed using well-chosen statistical methods and tests. The writing style is clear, concise and scientific.

Results (37 pp.)

The results of the author's own research are presented systematically and are well illustrated with 25 tables, 16 figures and 4 appendices, which attest to the quality of the research work.

Through the present work, data are presented for the first time in Bulgaria on the clinical and laboratory profile of PCOS in adolescence, on cut-off values for the Ferriman-Gallwey score (FGS) (> 6), on the significance of HOMA-IR as a predictor of hirsutism severity, and on comorbidity, including the prevalence of overweight, obesity and cardiometabolic complications.

FAI (> 6.2) was established as the marker with the highest specificity and sensitivity. Cut-off values were determined for androstenedione and AMH as markers suitable for adolescence. Correlations and cause-and-effect relationships between AMH levels, androgens, and metabolic and cardiovascular parameters were studied.

Regarding comorbidity in PCOS, arterial hypertension was found in almost half of the girls studied, correlating positively with obesity, acanthosis nigricans, HOMA-IR and insulin levels, and negatively with SHBP levels. A high prevalence of impaired glucose homeostasis, insulin resistance, fasting hyperinsulinemia and hypertriglyceridemia with low HDL-C was found, depending mainly on obesity.

Among the microRNAs studied in girls with PCOS, miR-320-5p and miR-103a-5p showed the highest diagnostic specificity and sensitivity, while miR-15a-5p allowed differentiation from healthy girls and other androgen-related conditions. They were shown to be independent diagnostic markers for PCOS, positively associated with blood pressure (SBP), FGS and CRP, but not with hyperandrogenemia, glucose and lipid metabolism, or ovarian morphology.

Discussion (33 pp.)

The results obtained are compared in detail and consistently with current scientific knowledge on the problems studied, drawing on the numerous sources in the bibliography. The presentation reveals the author's analytical and critical interpretation of the differences found.

Conclusions, contributions and summary (7 pp.)

I fully accept the conclusions of the dissertation, formulated by the researcher in 4 groups. They are presented in a logical sequence and with clear explanation.

Assessment of the publications

In connection with the dissertation, 4 publications are presented – 3 in international journals and 1 in a Bulgarian journal – with Dr. Mladenov as lead author. The publications are sufficient according to the regulations of the Medical University of Varna for the educational and scientific degree “Doctor”.

Appendices (8 pp.), 4 in total. This section presents evidence of approval by the Research Ethics Committee of the Medical University of Varna and the study instruments.

Bibliography (19 pp.) The reference list is extensive, containing 180 literature sources, 4 in Cyrillic and 176 in Latin script. There are no duplicates, and sources from the last 10 years are sufficiently represented.

3. Assessment of the results

The results of the research are significant and scientifically substantiated. They add to the knowledge of the clinical and laboratory characteristics of PCOS in adolescence, provide valuable data on comorbidity and enrich the diagnostic criteria. They confirm established patterns in the world literature that define PCOS as a complex and multifaceted challenge in pediatric endocrinology.

4. Assessment of the contributions

The contributions of the dissertation are mainly of a scientific and applied nature. For the first time in Bulgaria, and for the second time worldwide, the expression of selected microRNAs has been studied as diagnostic markers in girls with PCOS and in healthy girls, and for 4 of them this is the first such study in the world. Cut-off values of AMH, androstenedione and FAI for adolescence are presented for the first time in Bulgaria. With a focus on clinical practice, the diagnostic algorithm for PCOS in adolescence is enriched with new highly specific and sensitive biomarkers.

5. Critical remarks

No significant weaknesses or ambiguities can be pointed out; all requirements for the preparation of the dissertation have been met. Given the limited number of participants and the relatively small size of the control groups, appropriate non-parametric tests and methods have rightly been applied.

6. Conclusion

The dissertation of Dr. Vilhelm Mladenov is a large-scale study of a topical problem in pediatric endocrinology, focusing on polycystic ovary syndrome with onset in adolescence. Through its meticulous execution, comprehensive data with a detailed clinical and laboratory assessment of PCOS are provided for the first time in Bulgaria, and cut-off values for AMH, androstenedione and FAI for this age group have been determined. The diagnostic criteria are enriched with new highly specific biomarkers (microRNAs), studied for the first time in Bulgaria and for the second time worldwide, with 4 of them studied for the first time in the world.

It is confirmed that patients with PCOS have a high incidence of overweight, obesity and cardiometabolic complications. The need for personalized early interventions to prevent these complications is demonstrated. The healthcare system is provided with the facts and evidence needed for the National Health Insurance Fund (NHIF) to include FAI, androstenedione and AMH as appropriate diagnostic criteria for PCOS in adolescence. The present dissertation can

serve as a basis for future larger-scale studies and for the development of a National Consensus on the diagnosis and treatment of PCOS in girls up to 18 years of age.

With the present work, Dr. Vilhelm Ruslanov Mladenov shows that he possesses the necessary theoretical knowledge and professional skills and demonstrates the qualities required to conduct scientific research independently.

In scientific terms, the dissertation meets the requirements of the Act on the Development of the Academic Staff in the Republic of Bulgaria (ADASRB), the Regulations for its implementation, and the Regulations on the Development of the Academic Staff at the Medical University of Varna.

In view of the above, I give a positive assessment of the dissertation and propose that the esteemed Scientific Jury award Dr. Wilhelm Ruslanov Mladenov the educational and scientific degree "Doctor" in the scientific specialty "Pediatrics" (03.01.50).

28.09.2026
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Prepared by:
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