

OPINION

By: Assoc. Prof. Dr. Chayka Kirilova Petrova, PhD
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Subject: Dissertation of Dr. Teodora Rosenova Karamfilova, full-time PhD student at the Department of Pediatrics, Medical University – Varna, submitted for the award of the Educational and Scientific Degree “Doctor” in the field of Higher Education 7. Healthcare and Sports, professional field 7.1. Medicine, Doctoral Program “Pediatrics”.

According to Rector’s Order No. P-109-405/01.10.2025 and the decision of the Scientific Jury (Protocol No. 1/03.10.2025), I have been appointed to prepare an opinion on the dissertation of Dr. Teodora Rosenova Karamfilova entitled **“Nonclassical Form of Congenital Adrenal Hyperplasia – A Mosaic of the Known and the Unknown”** for the award of the Educational and Scientific Degree “Doctor” in the professional field 7.1. Medicine, scientific specialty Pediatrics – code 03.01.50.

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

Biographical Data

Dr. Teodora Rosenova Karamfilova was born in 1992 in Kyustendil, Bulgaria. She graduated with distinction from the High School of Mathematics “Prof. Emanuil Ivanov” in 2011. She obtained her Master’s degree in Medicine from the Medical University – Varna in 2017.

In 2019 she was enrolled as a full-time PhD student at the Department of Pediatrics, MU–Varna. Since 2020 she has been working as a part-time assistant at MU–Varna (Bulgarian- and English-language programs). She obtained her specialty in *Pediatrics* in 2022 and has been a *Pediatric Endocrinology and Metabolic Diseases* resident since 2023. She has over eight years of professional experience as a pediatrician at the Department of Pediatric Intensive Care, First Pediatric Clinic, University Hospital “St. Marina” – Varna.

Her scientific interests are focused on rare endocrine disorders, genetic syndromes, growth disorders, and particularly on hyperandrogenism.

Dr. Karamfilova has participated in 8 research projects, received 3 academic awards (including one related to her doctoral research), and has attended specialized international trainings such as the ESPE Winter School (Belgrade, 2023). She has been an active participant in national and international scientific meetings of ESPE, ISPAD, BNSPE, and the Bulgarian Pediatric Association, and has completed certified courses in homeopathy and phytotherapy. She is a fellow under the National Program “Young Scientists and Postdoctoral Fellows” funded by the Ministry of Education and Science of Bulgaria.

Her scientific output includes 9 publications on rare diseases and hyperandrogenism (3 as first author) and numerous presentations at conferences in Bulgaria and abroad.

1. Evaluation of the Relevance of the Topic

Current research on Congenital Adrenal Hyperplasia (CAH) mainly addresses its classical forms associated with life-threatening adrenal insufficiency and severe hyperandrogenism. However, the nonclassical form of CAH (NCCAH) is one of the most frequent autosomal recessive disorders leading to androgen excess. Clinically, it often mimics other hyperandrogenic conditions, making diagnosis and management challenging.

During the past decade, attention has increasingly focused on the long-term consequences of chronic hyperandrogenism - particularly regarding cardiometabolic risk, body composition, fertility, and psychological wellbeing. Nevertheless, worldwide data on NCCAH, especially in children and adolescents, remain limited and often contradictory.

In Bulgaria, there are no comprehensive or systematic studies of NCCAH. The present dissertation therefore addresses an important gap in both scientific knowledge and clinical practice. The topic is highly relevant and innovative, with clear scientific and practical significance, and represents a pioneering study for the country.

2. Structure of the Dissertation

The dissertation is well organized and consists of 182 pages, covering all essential sections of a scientific thesis.

The literature review (35 pages) demonstrates the author's excellent expertise in the topic and capacity for critical interpretation of scientific sources. It presents a detailed discussion of the epidemiology and genetics of NCAH, the mechanisms of steroidogenesis, and the clinical manifestations of hyperandrogenism. The author analyzes the impact of chronic androgen excess on body composition (fat and lean mass, bone mineral density), insulin resistance, cardiometabolic risk, brain and psychological function, and quality of life. Special attention is given to the metabolic role of leptin and adiponectin and to the effects of long-term glucocorticoid therapy.

The aim and objectives (3 pages) are clearly formulated and operationalized into 8 specific research tasks.

The materials and methods section (12 pages) describes a case-control study involving 68 females aged 10–27 years (mean 15.6 ± 3.3 years), including 34 patients with NCCAH and 34 healthy controls, conducted from 2019 to 2022 at the First Pediatric Clinic, University Hospital "St. Marina" – Varna. Inclusion and exclusion criteria are well defined. The doctoral candidate actively participated in all stages of the research. The study was supported by a scientific project of MU–Varna. Statistical analyses were performed using appropriate and validated methods. The style is concise, clear, and scientific.

The results (37 pages) are presented systematically and supported by 36 tables, 11 figures, and 7 appendices, confirming the quality of data processing and analysis. For the first time in Bulgaria, the dissertation provides data on the clinical presentation and severity of hyperandrogenism in both treated and untreated patients with NCCAH. It validates the Ferriman–Gallwey score as a reliable monitoring tool and identifies androstenedione and 17-OHP as key predictors of symptom severity.

Auxological analysis showed no significant differences in BMI or waist circumference, although one-third of patients were overweight or obese (with abdominal obesity in some). Cardiometabolic indicators were largely similar between groups, yet correlations emerged between obesity, the degree of hirsutism, diastolic blood pressure, and androgen levels. Elevated androstenedione and 17-OHP were associated with increased cardiometabolic risk. Biomarker analysis revealed correlations between CRP and waist circumference/FGS, leptin and waist circumference, and adiponectin and HOMA-IR, DHEA-S, testosterone, confirming the antagonistic relationship between these adipokines. Body composition analysis showed lower bone mineral density and fat mass in NCCAH patients, with positive correlation between bone density and lean mass. Significant relationships between hormonal and body composition parameters were observed. Psychological assessment indicated poorer mental health and lower quality of life in NCCAH patients, correlated with the degree of hyperandrogenism.

The discussion (25 pages) presents a detailed and critical comparison of the obtained data with current international literature, demonstrating the author's analytical thinking and scientific maturity.

The conclusions and contributions (6 pages) are logically structured, concise, and fully supported by the empirical findings.

3. Evaluation of the Results

The results are scientifically sound, coherent, and well substantiated. The dissertation contributes to the understanding of the clinical heterogeneity of hirsutism in NCCAH, identifies biomarkers of cardiometabolic risk, and highlights the need for a multidisciplinary approach in patient management. The research also provides the first Bulgarian data on the psychological health and quality of life of NCCAH patients and assesses the impact of glucocorticoid therapy on these outcomes.

4. Scientific Contributions

The dissertation's contributions are primarily of applied scientific significance: For the first time in Bulgaria, it offers a comprehensive assessment of metabolic risk and body composition in patients with NCCAH. It explores the relationship between hyperandrogenism, metabolic markers, psychological health, and quality of life. It identifies predictive biochemical and hormonal indicators for cardiometabolic complications. It provides clinical insight into the adverse effects of glucocorticoid therapy and emphasizes the need for structured patient monitoring. The findings can inform future research, clinical practice, and national healthcare policies regarding rare endocrine disorders.

5. Critical Remarks

No major weaknesses or methodological flaws have been identified. All academic, ethical, and formal requirements have been duly observed.

6. Conclusion

The dissertation of Dr. Teodora Rosenova Karamfilova represents a comprehensive and pioneering study on a highly relevant problem in Pediatric Endocrinology, addressing a significant research gap in Bulgaria and contributing original data to international science.

The work systematically investigates NCCAH a condition with high prevalence but challenging diagnosis due to its overlap with other hyperandrogenic disorders. It convincingly demonstrates that chronic hyperandrogenism is a determinant of cardiometabolic, reproductive, and psychosocial disturbances, and that prolonged glucocorticoid therapy entails additional health risks.

The dissertation provides scientific evidence for developing a practical diagnostic and follow-up algorithm to prevent late complications in NCCAH.

Dr. Karamfilova demonstrates excellent theoretical knowledge, methodological competence, and professional maturity necessary for independent scientific research.

The dissertation fully meets the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, its Implementing Regulations, and the Regulations of the Medical University – Varna.

Based on the above, I give a positive evaluation of the dissertation and propose that Dr. Teodora Rosenova Karamfilova to be awarded the Educational and Scientific Degree “Doctor” in the scientific specialty Pediatrics (03.01.50).

Pleven, 17 October 2025

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