

To the Chair of the Scientific Jury
appointed by Order No. P-109-405/01.10.2025
of the Rector of the Medical University of Varna

OPINION

by
Assoc. Prof. Margarita Alexieva Arshinkova, MD, PhD
Department of Pediatrics, Medical University of Sofia
External member of the Scientific Jury

on the dissertation thesis entitled
“Nonclassical Form of Congenital Adrenal Hyperplasia – A Mosaic of the Known and the Unknown”
submitted by **Dr. Teodora Rosenova Karamfilova**
for the acquisition of the educational and scientific degree **Doctor**

Field of Higher Education: **7. Healthcare and Sports**
Professional Field: **7.1. Medicine**
Scientific Specialty: **Pediatrics**
Form of Doctoral Studies: **Full-time**
Medical University “Prof. Dr. Paraskev Stoyanov” – Varna
Scientific Supervisor: **Assoc. Prof. Sonya Vasileva Galcheva, MD, PhD**

Compliance with regulatory requirements

The materials submitted by Dr. Teodora Rosenova Karamfilova fully comply with the requirements of the Statute of the Medical University of Varna, the Law on the Development of the Academic Staff in the Republic of Bulgaria, and the Regulations for the acquisition of the PhD degree.

The dissertation has been discussed, approved, and submitted for defense by the Head of the Department of Pediatrics, Faculty of Medicine – Varna, based on the decision of the Departmental Council (Protocol No. 46/29.09.2025) and the decision of the Faculty Council of the Faculty of Medicine (Report No. 103-6377/30.09.2025).

Biographical information about the doctoral candidate

Dr. Teodora Rosenova Karamfilova was born on March 3, 1992, in Kyustendil, Bulgaria, where she graduated with distinction from the High School of Mathematics “Prof. Emanuil Ivanov.” In 2017, she obtained a Master’s degree in Medicine from the Medical University “Prof. Dr. Paraskev Stoyanov” – Varna.

In 2019, she was admitted as a full-time PhD student at the Department of Pediatrics, MU–Varna, and since 2020, she has served as an assistant lecturer, actively participating in the teaching of medical students, interns, and residents in both Bulgarian and English.

In 2022, she obtained her medical specialty in Pediatrics, and she has more than eight years of professional experience as a pediatrician in the Pediatric Intensive Care Unit (PICU) at the First Pediatric Clinic, University Hospital “St. Marina” – Varna. Since 2023, she has been a resident in Pediatric Endocrinology and Metabolic Diseases.

Dr. Karamfilova has been repeatedly awarded a scholarship from the National Programme “Young Scientists and Postdoctoral Fellows” of the Ministry of Education and Science of the Republic of Bulgaria. In 2023, she participated in the ESPE Winter School in Pediatric Endocrinology in Belgrade, where she presented her research project. She has taken part in numerous scientific conferences and educational courses in Bulgaria and abroad, mainly in the field of pediatric endocrinology.

She is a member of several professional organizations, including the Bulgarian Medical Association, the Bulgarian Pediatric Association, the Bulgarian National Society for Pediatric Endocrinology, the Varna Society for Pediatric Endocrinology, and the European Society for Paediatric Endocrinology (ESPE).

Relevance and significance of the topic

Congenital adrenal hyperplasia (CAH) comprises a group of autosomal recessive inherited disorders resulting from enzymatic defects in steroidogenesis, leading to deficient cortisol and/or aldosterone synthesis and excess adrenal androgen production. Over 95% of CAH cases are caused by mutations in the CYP21A2 gene, encoding the enzyme 21-hydroxylase. The nonclassical form of CAH (NCAH) represents the mildest clinical phenotype, characterized by 30–50% residual enzyme activity, allowing normal basal cortisol and aldosterone production but increased synthesis of adrenal androgens and their precursors.

The dissertation addresses nonclassical CAH, a condition that may manifest during prepubertal, pubertal, or adult age, presenting with premature pubarche, hirsutism, acne, menstrual irregularities, anovulation, polycystic ovarian morphology, and disturbances in growth and bone maturation. In adult women, hirsutism and infertility are among the most prominent manifestations.

In recent years, growing attention has been directed toward the long-term metabolic consequences of chronic hyperandrogenism in women with NCAH. Studies suggest associations with metabolic syndrome, insulin resistance, dyslipidemia, arterial hypertension, central obesity, and type 2 diabetes mellitus. The relevance of this topic arises from both the relatively high prevalence and diagnostic challenges of NCAH, which often delay timely therapeutic intervention.

Furthermore, ensuring adequate quality of life and psychological support is crucial for the emotional well-being of affected girls and women. Understanding the pathophysiological interactions between hyperandrogenism, metabolic risk, body composition, and psycho-emotional health may contribute to developing more effective diagnostic and therapeutic strategies for clinical practice.

Structure of the dissertation

The dissertation is structured according to the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria and related regulations.

It consists of 182 standard pages, illustrated with 36 tables and 11 figures, and includes 262 bibliographic references (3 in Cyrillic and 259 in Latin script).

Structure overview:

- Introduction – 3 pages
- Literature review – 35 pages
- Hypothesis, aim, and objectives – 3 pages
- Research methodology – 13 pages
- Results – 57 pages
- Discussion – 25 pages
- Conclusions – 3 pages
- Contributions – 1 page
- Publications related to the dissertation – 1 page
- Summary – 2 pages

The literature review is comprehensive, reflecting deep familiarity with the current state of research on the epidemiology, pathophysiology, and diagnostic approaches to NCAH. The author discusses in detail the genotype-phenotype correlations, the association between CYP21A2 mutations and 17OHP levels, as well as the relationships with testosterone and androstenedione concentrations. The review highlights the growing importance of genetic testing and personalized medicine in diagnosis and prognosis. It also thoroughly analyzes the metabolic and reproductive implications of NCAH.

Aim, design and methods

The aim of the study was to assess the cardiometabolic risk, body composition, psychological perception, and quality of life in females diagnosed with nonclassical congenital adrenal hyperplasia, exploring their associations with clinical and/or biochemical hyperandrogenism, and to compare the results with those of healthy controls.

The study employed a case-control design, including 68 females aged 10-27 years with NCAH and 34 age- and sex-matched healthy controls, conducted over three years (2019–2022) at the First Pediatric Clinic, PICU, and related research units at University Hospital “St. Marina” – Varna.

Comprehensive clinical, laboratory, imaging, and densitometric assessments were performed, including evaluation of adipokines (leptin and adiponectin) due to their potential role in metabolic regulation. Data were processed using SPSS for Windows, version 25.0 (Chicago, IL, USA), with statistical significance set at $p \leq 0.05$.

The chosen methods are appropriate and sufficient to achieve the stated aims, ensuring valid statistical and scientific conclusions.

Results and discussion

The results are presented clearly and systematically, well-illustrated with tables and figures.

Main findings include:

- Serum androstenedione and 17OHP are significant predictive markers for hirsutism, acne, alopecia, and menstrual disturbances, independent of age and pubertal stage.
- Leptin levels correlate positively with waist circumference ($p = 0.048$), while adiponectin shows a strong association with pubertal stage, followed by DHEA-S, HOMA-IR, and testosterone levels ($p < 0.05$).
- Females with NCAH demonstrated significantly lower scores in all quality-of-life domains, particularly regarding physical and mental health ($p < 0.001$), compared to non-hyperandrogenic controls.

The discussion logically follows the presentation of results, providing in-depth interpretation and comparison with the literature. The author demonstrates scientific maturity, critical thinking, and methodological competence.

The conclusions correspond to the objectives and derive logically from the results, though some partially restate them.

The seven contributions of the dissertation arise directly from the findings and include the first Bulgarian study and one of the few internationally to comprehensively evaluate quality of life, body composition, and cardiometabolic risk in adolescent and young adult females with NCAH, thereby contributing original scientific value.

Evaluation of publications and individual contribution

The findings of the dissertation have been published in two peer-reviewed scientific articles, both with Dr. Karamfilova as first author, and presented at four international scientific conferences, meeting the requirements of the Medical University of Varna.

The dissertation is well-structured, linguistically accurate, and scientifically coherent. Figures and tables are clearly presented, and the terminology is used precisely. All research and analytical work have been personally carried out by the doctoral candidate.

Conclusion

The dissertation presents original scientific and applied results, satisfying the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, its Implementing Regulations, and the internal criteria of the Medical University of Varna.

Dr. Teodora Rosenova Karamfilova demonstrates profound theoretical knowledge, methodological competence, and independence in conducting scientific research.

Based on the above, I give my positive assessment of the presented dissertation and recommend that the Scientific Jury award the educational and scientific degree “Doctor” in Pediatrics to Dr. Teodora Rosenova Karamfilova.

Sofia, October 20, 2021

Assoc. Prof. Margarita Arslanova Arslankova, PhD
Department of Pediatrics, Medical University of Sofia

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