

OPINION

by Prof. Dr. Violeta Mihova Iotova, PhD, MD

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scientific specialty – pediatrics

re: dissertation for awarding the educational and scientific degree "Doctor", in the field of higher education 7. Health and Sports, professional field 7.1. Medicine and doctoral program "Pediatrics".

by Dr. Teodora Rosenova Karamfilova

pediatrician and trainee in pediatric endocrinology and metabolic diseases

at the First Children's Clinic with DOIL, St. Marina University Hospital - Varna

on the topic **"Nonclassical form of congenital adrenal hyperplasia - a mosaic of known and unknown"**

Doctoral program in Pediatrics

Scientific supervisor: **Assoc. Prof. Dr. Sonya Vasileva Galcheva, MD**, Department of Pediatrics, MU-Varna

On the basis of an Order of the Rector of MU-Varna No. P-109-405/01.10.2025 and by decision of the Scientific Jury (Protocol No. 1/ 03.10.2025) I am appointed to prepare an opinion regarding the dissertation of Dr. Teodora Rosenova Karamfilova on the topic "Non-classical form of congenital adrenal hyperplasia - a mosaic of known and unknown" for the award of the educational and scientific degree "Doctor" in professional field 7.1 Medicine, scientific specialty "Pediatrics". The opinion has been prepared in accordance with the requirements of the Act on the Development of the Academic Staff in the Republic of Bulgaria, Chapter II , Section I of the PPZRASRB, as well as the Regulations for its implementation at the Medical University - Varna.

1. General presentation of the procedure

The presented set of materials is in accordance with the above-mentioned law and regulations, and includes all necessary documents.

2. Presentation of the doctoral student

Dr. Teodora Karamfilova was born in 1992 in the town of Kyustendil. She graduated with honors from the Medical University "Prof. Emanuel Ivanov" in Kyustendil. In 2017, she obtained a Master's degree in Medicine from the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna and almost immediately started working as a doctor in the Emergency Department - Children at the University Hospital "St. Marina" - Varna. Since 2018 , she has been part of the team of the Children's

Intensive Care Unit. In 2019, after a successful competition, she was enrolled as a full-time doctoral student at the Department of Pediatrics, MU-Varna, with Assoc. Prof. Sonya Galcheva as her scientific supervisor. Since 2020, Dr. Karamfilova has been a full-time assistant at MU-Varna (BEO and AEO). She obtained a specialty in pediatrics in 2022, and in 2023 she was enrolled as a trainee in pediatric endocrinology and metabolic diseases. In 2026, she will take an exam to acquire this specialty.

After graduating, Dr. Teodora Karamfilova participated in a total of 8 scientific and applied science projects, one of which won by her in the extremely competitive environment of the Science Fund at MU-Varna. She has already received a scientific award and successfully won funding for part of her doctoral studies from the Science Fund of MU-Varna. She pays great attention to her education and scientific activity, participating in the ESPE Winter School, Belgrade, 2023; in congresses and annual scientific meetings of the European Society of Pediatric Endocrinology (ESPE), the International Society of Pediatric and Adolescent Diabetes (ISPAD), the Bulgarian National Society of Pediatric Endocrinology (BNSPE), the Varna Society of Pediatric Endocrinology (VAPES), Bulgarian Pediatric Association, etc. Dr. Karamfilova is a scholarship holder from the National Program "Young Scientists and Postdoctoral Fellows" at the Ministry of Education and Science of the Republic of Bulgaria for several consecutive years, as well as a scholarship holder at the Ministry of Health as a trainee in a rare specialty from 2025. Her scientific output to date is primarily in the field of rare endocrine diseases and includes 9 articles.

3. Relevance of the topic and appropriateness of the goals and objectives set

Congenital adrenal hyperplasia (CAH) is a spectrum of hyperandrogenic disorders of varying severity. While some of its forms are very severe and life-threatening, others cause more psychological disorders and deviations in the quality of life. Nonclassical CAH (NCAH) falls into the latter. In this case, the manifestations of hyperandrogenism are less pronounced, but with the potential to cause hormonal and skin manifestations, reflecting on the appearance of those affected, but also on their hormonal status, pubertal development and final height, most often in the form of failure to reach the genetically determined final height. Its clinical recognition in girls and women is still difficult, as is its differentiation from the other common form of hyperandrogenism in girls and women, "Polycystic Ovary Syndrome (PCOS)". There is debate about the most appropriate drug treatment and follow-up, and almost nothing is known about the long-term fate of these girls and women. The male gender is even more neglected, as the manifestations and consequences of the condition of NCAH in boys and men are almost completely unknown at the moment. In our country, no systematic scientific study of patients with NCAH has been conducted to date, especially with a focus on metabolic manifestations and long-term consequences. As far as we know, a study on the psychological well-being and quality of life among girls with hyperandrogenism has not been conducted in our country, and there is almost no such study in the world literature, specifically focused on NCAH.

The dissertation proposed for defense is a pilot for the country, and in some aspects also for the international scientific space, and lays the foundation for future development in this scientific field. It is not only relevant, but also has scientific and applied potential for improving knowledge, diagnostic success, and improving the fate of these patients.

4. Characteristics and evaluation of the dissertation work

Dr. Karamfilova's dissertation is presented on 182 standard pages and is illustrated with 36 tables, 11 figures and 7 appendices, fully objectifying the high standards in carrying out the scientific work. The bibliography contains 262 sources, of which 3 in Cyrillic and 259 in Latin languages. No significant repetitions are noticeable. The sources from the last 10 years are over 40%, which proves the relevance of the topic and the contemporary view of the dissertation. This is also the reason for the very few sources in Bulgarian.

The literature review is pleasant to read, clear and purposeful. It shows a good command of the material, careful selection, fully related to the chosen topic and a desire for correct interpretation of the sources. The doctoral student has presented in depth and with detailed analysis the development of knowledge about the disease, including the genesis of hyperandrogenism and its known effects on body composition and the cardiovascular system. Attention is paid to all factors contributing to health organic and psychological problems. In addition to the already well-known metabolic processes, the doctoral candidate draws attention to the most frequently studied adipokines leptin and adiponectin and their relationship to hyperandrogenism in non-classical congenital adrenal hyperplasia. Glucocorticoid therapy and its possible, including adverse effects, are not omitted.

A particularly valuable part of the Review are the prerequisites for the scientific research, which demonstrate the thorough and responsible approach taken by Dr. Karamfilova and her scientific supervisor to the choice of the topic and object of the study.

The goal is clearly formulated, and the tasks related to it are well structured and detailed enough to allow for their proper implementation.

The most important part of the success of a scientific paper is its **methodology**. In the presented work, the entire process of selecting the type of scientific study (case-control), age of the subjects, inclusion and exclusion criteria, number of participants, methods and instruments of the study, statistical processing of the results are presented in detail, competently and convincingly. Girls and young women up to 30 years of age with proven childhood NCAH according to the standard currently generally accepted criteria were included. The majority of the subjects were on treatment, mainly with glucocorticoids. All ethical requirements for conducting a scientific study were met, and the relevant documents were presented as evidence.

The results are presented consistently, well illustrated and very useful, also from a clinical point of view. For the first time in our country, data on the degree of hyperandrogenism in treated and untreated patients with NCAH are generated. The importance of the Ferriman-Gallwey score as a reliable tool for diagnosis and clinical monitoring of the condition is recalled. Of the hormonal factors, not only is the importance of the known androstenedione and 17 -OH-Progesterone confirmed as the most correlated with the degree of clinical symptoms, but the lack of significant importance of DHEAS, still a widely studied androgen with a low degree of correct interpretation in clinical practice, is also emphasized.

The changes in cardiometabolic markers in patients are not unexpected, rather the contribution is in the discovery of existing differences with unaffected controls at this early age. Using

statistical methods, a relationship has been demonstrated between some adrenal androgens and blood pressure values, overweight and the severity of hirsutism.

Other important results are the data on the anthropometric parameters of the subjects, body composition and bone density. Despite the high level of androgens, a significant part of the participants demonstrated a tendency to obesity, including abdominal obesity. Relationships were found between metabolic and cardiovascular risk markers (CRP, SHBG, HOMA-IR, etc.) and hormonal values. The expected lower content of adipose tissue was objectified, but with lower values for bone mineral density. The latter finding cannot be clarified within the framework of the present study, but provides directions for future research. There is a complex interaction between the components of the TC and hormonal indicators: positive correlation between adipose tissue (AT) and 17-OH-Progesterone; negative correlation between AT and fat-free AT with SHBG, as well as AT with cortisol.

Psychological assessment shows poorer mental health compared to controls. Of importance is hyperandrogenism (hirsutism), which negatively correlates with lower quality of life in patients with NCAH.

The **discussion** consistently examines own results in comparison with the contemporary scientific research well-known to the candidate. We want to emphasize again that there are no significant repetitions with the references of the review. In addition to the facts being presented objectively and without undue weighting by the author, they are interpreted in the most objective way possible at the moment according to the level of scientific knowledge. The dissertation candidate skillfully handles the literature data and her own results and manages to find a scientific explanation for them. Thus one not only obtains additional information about the NCAH, but new directions of scientific research are followed, which is very useful for the readers.

In formulating **the conclusions** the sequence of the tasks was precisely followed, with a total of 21 conclusions being drawn for the 8 tasks. They accurately and objectively present the results obtained. They could be further summarized, thus demonstrating the doctoral candidate's additional capabilities for synthesizing scientific results. Nevertheless, we accept the conclusions as credible.

Dr. Karamfilova presents **7 contributions** to her dissertation work, without dividing them into those of an original and those of a confirmatory nature. Due to the scarce literature knowledge about NCAH, especially in adolescence, all the results obtained are a scientific contribution. The data on the psychological state and quality of life in patients are particularly valuable. The dissertation ends with an analytical and interesting conclusion, which represents a kind of plan for future research. All the more significant scientific instruments of the study are presented as appendices, which is particularly valuable because it allows for replication of the results in the future, respectively their validation.

The dissertation has been accompanied by 2 articles in refereed journals in Bulgaria and 4 scientific communications abroad. According to the Regulations for the Development of the Academic Staff of MU-Varna, the articles and scientific contributions fully meet the requirements for acquiring the educational and scientific degree "doctor".

In summary, the results of Dr. Teodora Karamfilova's dissertation are contemporary, scientifically sound and significant for the international scientific community and for our local science and clinical practice. They represent a scientific contribution, in which the data on the mental state and quality of life of patients with NCAH, cardio-vascular and metabolic risk factors, their correlation

with hormonal and anthropometric parameters, and last but not least – the proven safety of long-term treatment with glucocorticoids stand out. The recommendation for deriving algorithms for differential diagnosis, treatment and follow-up of these patients is very timely and necessary.

I don't have any critical comments but strongly urge the doctoral candidate to publish her most significant results in the international scientific literature. I also use this opportunity to draw her attention to the even less scientifically and clinically understood group of male individuals affected by NCAH, which also needs a more systematic approach in the near future.

Conclusion

In conclusion, I am convinced that Dr. Teodora Karamfilova's dissertation is an extremely timely and significant insight into the clinical features, risks and problems of girls with NCAH. The work is well thought out, structured, with clearly formulated and implemented tasks. Its conclusions are accurate and logical, and the contributions are formulated very thoroughly. The dissertation represents an excellent basis for further research and improvement of care for this group of patients, including those of the male sex. The scientific work is carried out precisely and modernly, with the intelligence, determination and responsibility inherent in the dissertation candidate and to her scientific supervisor.

The dissertation meets all the requirements of the Act on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its Implementation and the relevant Regulations at the Medical University - Varna.

All this gives me reason to confidently recommend to the members of the esteemed Scientific Jury to award Dr. Teodora Rosenova Karamfilova the educational and scientific degree of "doctor".

21.10.2025

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Заличено на основание чл. 5,
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/Prof. Dr. V. Iotova/