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STATEMENT

Assoc. Prof. Sonya Vassileva Galcheva, MD, PhD
Pediatric Endocrinologist, Department of Pediatrics, Medical University "Prof. Dr. Paraskev Stoyanov," Varna

Regarding the Dissertation

of Dr. Nikolinka Yordanova Peykova

on the topic

"Metabolic Risk and Body Composition in Children Born Small for Gestational Age Due to Genetic Syndromes (Prader-Willi, Silver-Russell, and Others)"

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

Scientific Supervisor:

Prof. Violeta Mihova Yotova, MD, PhD

Based on Order No. R-109-362/28.10.2024 issued by the Rector of the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna, and following the decision of the Scientific Jury as per Protocol No. 1/04.11.2024, I have been assigned to prepare a statement (in both Bulgarian and English) on the dissertation titled: "Metabolic Risk and Body Composition in Children Born Small for Gestational Age Due to Genetic Syndromes (Prader-Willi, Silver-Russell, and Others)."

This statement is prepared in accordance with the Law on the Development of the Academic Staff in the Republic of Bulgaria and the Regulations for the Development of Academic Staff at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna.

The procedural stages of the doctoral training have been duly followed, with no changes to the initial topic or the scientific supervisor. The candidate has submitted all required documents and materials in compliance with the procedural requirements for obtaining the educational and scientific degree "Doctor" as stipulated in the regulations of the Medical University - Varna. .

1. Brief Biographical and Professional Data for the Candidate.

Dr. Nikolinka Yordanova was born on June 1, 1990, in the city of Yambol, where she graduated with honors from the "Atanas Radev" Mathematics High School. In 2015, she completed her Master's degree in Medicine at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna. In 2020, she obtained a specialization in "Pediatric Endocrinology and Metabolism." In 2019, she won a competitive position as a full-time doctoral student in the Department of Pediatrics at the Medical University - Varna, under the supervision of Prof. Violeta Yotova, MD, PhD.

Since 2020, she has been a part-time assistant in the Department of Pediatrics at the Medical University - Varna, actively involved in teaching students, interns, and residents in both English and Bulgarian. Dr. Yordanova also works as a pediatric endocrinologist at the First pediatric clinic, University Hospital "St. Marina" EAD - Varna. She quickly developed the skills required for preparing and conducting her dissertation research.

Dr. Yordanova's clinical and scientific interests are primarily focused on rare endocrine disorders. She leads a multidisciplinary care team for patients with Prader-Willi and Silver-Russell syndromes at the Expert Center for Rare Endocrine Diseases at University Hospital "St. Marina" EAD, which is part of the European Reference Network for Rare Endocrine Diseases (Endo-ERN). She has participated in numerous national and international scientific schools and courses. In 2022, she undertook a one-month specialization at Erasmus MC Sophia Children's Hospital in Rotterdam, the Netherlands, focusing on the specific care of patients with rare imprinting syndromes (Prader-Willi and Silver-Russell syndromes), funded by the European Reference Network for Rare Endocrine Diseases (Endo-ERN).

She has been awarded grants three times by the International Prader-Willi Syndrome Organization (IPWSO) to participate in international congresses and family conferences of the organization (Cuba, 2019; Ireland, 2022; USA, 2025). Dr. Yordanova is a member of several professional societies and organizations, including the Bulgarian Medical Association, the Bulgarian Pediatric Association, the Bulgarian National Association for Pediatric Endocrinology, the Varna Pediatric Endocrinology Society, and the European Society for Pediatric Endocrinology.

2. Relevance of the Topic

Prader-Willi Syndrome (PWS) and Silver-Russell Syndrome (SRS) are rare endocrine disorders with distinct clinical and diagnostic features, resulting from a genetic defect associated with disrupted genomic imprinting.

Both syndromes exhibit overlapping clinical characteristics, including low birth weight and alterations in body composition. These changes are linked to an elevated risk of early-onset cardiometabolic disturbances and conditions such as cardiovascular disease, hypertension, dyslipidemia, obesity, insulin resistance, and type 2 diabetes mellitus. Treatment with recombinant human growth hormone (rhGH) has been scientifically validated to improve body composition by increasing the proportion of lean body mass.

The comprehensive investigation of clinical and laboratory characteristics in patients with these imprinting syndromes, along with an in-depth analysis of the potential interrelationship between body composition and metabolic profile, represents a critical area of interest in modern endocrinology and the study of rare diseases. Such research holds the potential to optimize patient care for individuals with PWS and SRS and significantly enhance their quality of life.

At the initiation of Dr. Yordanova's research, no other scientific study in Bulgaria had undertaken an extensive exploration of the clinical and laboratory profiles of PWS and SRS patients, with a specific focus on the correlation between their body composition and muscle mass. Furthermore, no prior work had evaluated the quality of life of these patients who are monitored and treated within the framework of the Expert Center for Rare Endocrine Diseases.

For these reasons, the chosen dissertation topic is highly relevant, innovative, and of profound importance, both for advancing scientific knowledge and for improving clinical practice.

3. Characteristics, Scope, and Structure of the Dissertation

Dr. Nikolinka Yordanova's dissertation spans 158 pages and is illustrated with 30 tables and 8 figures. It is written in well-structured Bulgarian, showcasing an excellent command of highly specialized terminology. The dissertation is organized into the following main sections:

3.1. Literature Review (37 pages)

The literature review is exceptionally well-structured, divided into two subsections, systematically presenting findings from global research on the primary characteristics of the two syndromes. It provides an in-depth analysis of existing data regarding prevalence, historical background, etiology, diagnostic methods, phenotypic dysmorphism, associated clinical and laboratory characteristics, treatment approaches, complications, mortality causes, quality of life, and the psychosocial aspects of Prader-Willi Syndrome (PWS) and Silver-Russell Syndrome (SRS). The clinical and laboratory parameters contributing to elevated cardiometabolic risk in patients with these imprinting disorders are comprehensively analyzed. The dissertation demonstrates the candidate's excellent theoretical knowledge and familiarity with the most recent advances in the field.

3.2. Premises, Aim, and Objectives (2 pages)

The thorough and analytical review of the literature, combined with the candidate's excellent understanding of the scientific context, led to the formulation of six premises supporting the clear definition of the dissertation's research aim: to evaluate cardiovascular and metabolic risks in patients with PWS and SRS based on their fat and muscle mass composition.

To achieve this aim, the dissertation outlines four clearly formulated objectives, reflecting the structured and focused approach to addressing the research problem.

3.3. Original Research – Participants and Methods (10 pages)

To fulfill the dissertation's aim and objectives, two parallel cross-sectional case-control studies were conducted. The study design, participant number (82 total, including 25 PWS patients, 18 SRS patients, and 39 healthy controls matched by sex, age, and partially by BMI),

inclusion and exclusion criteria, and the methods used to address the research objectives are clearly and competently presented by the candidate.

The research was conducted in full compliance with the principles of good scientific practice, following ethical approval from the Ethics Committee on Research at the Medical University of Varna. Parental informed consent forms for child participation were duly obtained.

The statistical methods were appropriately selected and ensured the reliable analysis of the data obtained.

3.4. Original Results (27 pages)

In this section, Dr. Yordanova provides a detailed description and demonstrates the successful completion of each task related to achieving the primary aim of her scientific work. The results are well-illustrated with numerous figures and tables, accompanied by clear and comprehensible text. The chosen statistical methods for analysis are appropriate and correctly applied.

The results are presented separately for the two syndromes and organized into five subsections:

- Subsection 1: Analysis of demographic, auxological, and clinical characteristics of participants, including comparisons of parameters between patients and their respective controls from the corresponding sub-study, with an evaluation of genetic diagnoses.
- Subsection 2: Analysis of diagnostic risk factors, criteria, and family history.
- Subsection 3: Analysis of biochemical, metabolic, and hormonal parameters, with a comparison of data between the two subgroups.
- Subsection 4: Analysis of body composition and the distribution of fat and lean mass, with a comparison of data between the two subgroups.
- Subsection 5: Assessment of quality of life in both patient groups.

3.5. Discussion, Conclusions, and Contributions (28 pages)

In this section, Dr. Yordanova again demonstrates her deep knowledge of global scientific literature on the topic by appropriately discussing and comparing her findings with those from other national and international studies. She shows transparency and a critical perspective regarding some of the limitations of her research—qualities that I highly appreciate.

Fifteen conclusions (eight for the PWS subgroup and seven for the SRS subgroup) are formulated in a logical and consistent manner, aligned with the results obtained and the research objectives.

The dissertation outlines eight contributions of both scientific and practical significance, five of which are original and highlight the importance of this work. These contributions encapsulate the value of the dissertation in advancing knowledge and clinical practice in the field.

3.6. References (20 pages)

The reference list comprises 382 sources, of which 11 are in Cyrillic and 371 in Latin script, with 180 published within the past decade.

Publications and Scientific Contributions

Dr. Yordanova has provided a list of two full-text publications directly associated with her dissertation and two presentations at international scientific conferences. Her research activity adheres fully to the regulatory requirements for the attainment of the educational and scientific degree of "Doctor."

Summary

The dissertation summary spans 100 pages and is meticulously structured in accordance with established academic standards. Its content is fully aligned with the substance of the dissertation.

Critical Observations

I have no critical observations to report.

CONCLUSION

The dissertation submitted for evaluation represents an original scholarly contribution by the author, distinguished by its relevance, depth, and rigorous engagement with the research domain. It further demonstrates significant scientific and practical applicability.

Dr. Nikolinka Yordanova is an excellent and empathetic pediatric endocrinologist, fully dedicated to her work with children and personally engaged with the challenges faced by families of children with Prader-Willi and Silver-Russell syndromes. During her research, she demonstrated immense effort, patience, perseverance, and resilience, which, despite significant personal bereavement, enabled her to successfully conduct and complete a valuable and in-depth scientific study..

Based on the foregoing considerations, I unequivocally provide a positive assessment and strongly recommend that the esteemed Scientific Jury confer upon Dr. Nikolinka Yordanova Peykova the academic degree of "Doctor."

22.11.2024

Varna

Prepared by

Assoc. Prof. Sonya Vasileva Galcheva, MD, PhD

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