

REVIEW

by

Prof. Dr. Elena Galabova Poryazova-Markova, MD

Department of General and Clinical Pathology

Faculty of Medicine, Medical University - Plovdiv

on the dissertation for the award of the educational and scientific degree "Doctor"

Professional field: 7.1. "Medicine"

Field of higher education: 7. Health and sports

Doctoral program: "Obstetrics and Gynecology"

Dissertation candidate: Dr. Krum Stefanov Vladov

Form of doctoral studies: full-time

Department of "Obstetrics and Gynecology" of the Medical University - Plovdiv

Topic: "Analysis of the expression of hormone receptors and the biomarkers p53 and Ki-67 in endometrial polyps in pre- and postmenopausal women"

Scientific supervisors: Prof. Dr. Ekaterina Uchikova, MD.

Prof. Dr. Veselin Belovezhov, MD

1. General presentation of the procedure and the doctoral student

This review was prepared based on Order No. R-3342/01.07.2025 of the Rector of the Medical University-Plovdiv and Protocol of the Faculty Council No. 6/18.06.2025 of the Medical Faculty for the appointment of a scientific jury and the conduct of the defense of a dissertation.

The set of materials presented to me by Dr. Krum Stefanov Vladov in electronic and paper format is in accordance with the Regulations for Academic Development

and the terms and conditions for acquiring the ONS "Doctor" at the Medical University - Plovdiv and meet the requirements of the ZRASRB. The doctoral student has attached six publications related to the topic of the dissertation, one of which is in print, as well as three participations in scientific forums.

2. Brief biographical data about the doctoral student

Dr. Krum Stefanov Vladov was born on 12.04.1992. He graduated with honors from the Medical University - Plovdiv in 2017. He works as a specialist doctor in the Clinic of Obstetrics and Gynecology of the University Hospital "St. George" from 2017 to 2021. In 2022, he acquired a specialty in Obstetrics and Gynecology. He is a part-time lecturer for the purposes of English-language training of students in the specialties of medicine and dentistry during the academic year 2019-2020. Since November 2020 and currently works as an Assistant at the Department of Obstetrics and Gynecology of the Faculty of Medicine, Medical University - Plovdiv. He participates in the training of fourth, fifth and sixth year students in the specialties of medicine and dentistry in Bulgarian and English. He teaches intern doctors, as well as students under the Erasmus program. He participates as a lecturer with reports and presentations at scientific congresses and conferences. He is a lecturer in the basic course "Selected Chapters from Obstetrics and Gynecology" first and second parts, organized by the Department of Obstetrics and Gynecology, intended for postgraduate students. He is the organizer of the Obstetrics and Gynecology Circle for medical students.

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

The topic of Dr. Krum Vladov's dissertation is dedicated to endometrial polyps in pre- and postmenopausal women - a current and common pathology in gynecological practice. Endometrial polyps are well known in the daily practice of the pathologist as benign proliferative lesions. The criteria for assessing their malignant potential and their role as precancerous lesions in evolution into endometrial cancer are not fully known. Disorders in the mechanisms of cell proliferation and apoptosis and local inflammatory factors are considered as possible pathogenetic mechanisms. In recent years, a connection has been established between overweight, insulin resistance, diabetes mellitus, metabolic syndrome, arterial hypertension and the development of endometrial polyps.

According to the National Cancer Registry, endometrial carcinoma is in second place after breast carcinoma among oncological diseases in women in our country. As modern biomarkers for assessing the malignant potential of endometrial polyps, the literature indicates the immunohistochemical expression of steroid receptors, as well as the tumor suppressor gene p53 and the proliferative marker Ki-67. The aim of the study is to analyze the expression of estrogen and progesterone steroid receptors, the biomarkers p53 and Ki-67 in endometrial polyps in pre- and postmenopausal women. The five tasks set are clearly and precisely formulated. The results obtained lead to solving the set goals and tasks - clarifying the etiology, pathogenesis, risk of malignant transformation and progression to endometrial carcinoma of endometrial polyps, as well as the appropriateness of using hormonal therapy in pre- and postmenopausal women with concomitant risk factors.

4. Knowledge of the problem

The literature review, the clearly formulated goal and appropriately set tasks show that Dr. Vladov has convincing knowledge of the problem under consideration for the etiology, pathogenesis and evolution of endometrial polyps and stratification of the risk of malignancy by hormonal and proliferative biomarkers, as well as that he creatively evaluates the literature material. The study used modern molecular markers to assess the risk of malignant transformation of endometrial polyps, such as the tumor suppressor gene p53 and the proliferative marker Ki-67. Dr. Vladov shows in-depth theoretical knowledge and good practical skills for scientific research.

5. Research methodology.

By its nature, the study is applied, cross-sectional in design. It includes a study on 120 women hospitalized in the Clinic of Obstetrics and Gynecology of the University Hospital "St. George" - EAD, Plovdiv. The patients were divided into three groups, in which the following parameters were studied: serum levels of estradiol, menstrual (menarche, menopause) and reproductive factors (number of births, age at first birth), the expression of ER, PR, p53 and Ki-67.

Clinical and diagnostic research methods, classical histological and clinical-laboratory research methods were applied. Dr. Vladov investigated morphological aspects of the pathological process by analyzing the serum level of hormone

receptors and the immunohistochemical expression of tumor markers. In essence, the research methodology combines approaches from obstetrics and gynecology, molecular biology and clinical pathology. The statistical analysis was performed using the statistical package IBM SPSS Statistics, (version 26.0; SPSS, Inc., Chicago, IL, USA), which objectifies the results obtained.

6. Characteristics and evaluation of the dissertation work.

The dissertation work submitted to me for review has a total volume of 210 standard pages. It is illustrated with 56 figures and 82 tables. The bibliography includes 196 literary sources, of which 15 are in Bulgarian, half of them from the last 10 years.

The structure of the dissertation work includes the following parts: introduction, literature review, goal and tasks, materials and methods, own results, discussion, contributions and bibliography. The introduction briefly justifies the relevance and significance of the scientific problem under consideration. The literature review, in a volume of 37 pages, presents the main aspects and data in the scientific literature on the topic of the dissertation. The chapter "Goal and tasks" follows, in which the dissertationist sets a clear goal and 5 tasks logically related to it. The methodology correlates with the goal and the results lead to its realization. The results are presented on a total of 113 pages, explaining and analyzing the study in detail. The statistical analysis objectifies them. 6 conclusions are drawn from the results obtained. The dissertation has theoretical and scientifically applied original contributions.

7. Contributions and significance of the work for science and practice

The dissertation work of Dr. Krum Vladov, submitted to me for review, is a comprehensive study on the expression of hormone receptors, the biomarkers p53 and Ki-67 in endometrial polyps in pre- and postmenopausal women. Dr. Vladov's scientific work provides a new insight into the evolution and assessment of endometrial polyps, through the analysis of the expression of p53, Ki67, ER and PR, providing a valuable basis for differential diagnosis, assessment of the risk of malignant transformation and selection of an individualized therapeutic strategy. As the author points out, for the first time in Bulgaria, a comprehensive analysis of age, reproductive and menstrual factors, serum levels of estradiol, receptor steroid

expression and cellular biomarkers (Ki-67, p53) in women with endometrial polyps, endometrial carcinoma and atrophic endometrium has been carried out. Hypotheses have been formulated on the etiology and pathogenesis of endometrial polyps based on the results obtained. The biological inertness of the stromal component has been proven by the lack of expression of p53 and Ki-67 in the three studied endometrial pathologies.

8. Evaluation of the publications on the dissertation

Dr. Krum Stefanov Vladov has presented six publications related to the topic of the dissertation, five of which are in English. In five of the publications he is the first author, and in the last one he is part of the author team. A practical model for risk stratification in endometrial polyps has been proposed, based on a combination of clinical, hormonal, metabolic factors, as well as immunohistochemical examination, which allows for individual risk assessment and can be used when making a decision on subsequent clinical behavior.

9. Personal participation of the doctoral student

I believe that the implementation of this dissertation is entirely the work of the dissertation candidate Dr. Krum Vladov, both the analysis of the results obtained with the conclusions from them, and the formulated contributions.

10. Abstract

The abstract follows the logic of the dissertation work, is prepared according to the rules in a volume of 70 standard pages. In terms of content and quality, it reflects the main results achieved in the dissertation, with their conclusions and contributions.

11. Critical notes and recommendations

I have no critical notes for the doctoral student. I recommend that Dr. Vladov write a monograph and expand his publication activity.

12. Personal impressions

I know the dissertation candidate Dr. Krum Stefanov Vladov as a consistent and responsible colleague, scientist and teacher, a doctor with high professionalism and morality, with in-depth knowledge in his clinical and scientific specialty.

13. Conclusion

The dissertation work of Dr. Krum Vladov has theoretical and scientific-applied results, which represent an original contribution to science and meet all the requirements of the Act on the Development of the Academic Staff in the Republic of Bulgaria (ZRASRB), the Regulations for the Implementation of ZRASRB and the relevant Regulations of MU - Plovdiv. Due to the above, I give my **positive** assessment for the dissertation work and abstract reviewed by me. I vote **positively** for the award of the educational and scientific degree "doctor" to Dr. Krum Stefanov Vladov in the doctoral program "Obstetrics and Gynecology".

22/07/2025

Reviewer:



Заличено на основание
Чл.5 §1, 6. "В" Регламент (ЕС)2016/679

Prof. Dr. Elena Galabova Poryazova-Markova, MD