

Review for the educational and scientific degree “Doctor of philosophy”

МЕДИЦИНСКИ УНИВЕРСИТЕТ

ПЛОВДИВ

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of the doctoral thesis for the acquisition of the educational and scientific degree “Doctor of
Philosophy”

Professional Field: Medicine

Doctoral Program: Cardiology (code 03.01.47)

Author: Dolina Gencheva Gencheva, M.D.

Form of study: Independent

Title: „ASSESSMENT OF CHANGES IN CARDIAC STRUCTURE AND FUNCTION IN
PREGNANT WOMEN WITH PREECLAMPSIA AND GESTATIONAL HYPERTENSION”

Scientific advisors:

Prof. Fedya Nikolov, M.D., PhD

Prof. Ekaterina Uchikova, M.D., Ph

Scientific consultant:

Assoc. Prof. Krasimira Hristova, M.D., PhD

1. General introduction of the procedure and the PhD candidate

The presented set of documents in paper/electronic form is in accordance with Article 115 (1) of the Procedure for acquisition of the educational and scientific degree "Doctor of Philosophy" at Medical University - Plovdiv; the Regulations of Medical University - Plovdiv from 06.11.2014 and includes the following documents:

- Application to the Rector of Medical University - Plovdiv for a procedure for the defence of the doctoral thesis;
- Autobiography in European format with the PhD student's signature;
- Notarized copy of a diploma of higher education;
- Orders for the enrolment in a PhD and for the eligibility for public defense;
- Order for sitting an exam according to the individual plan and the protocol of the successfully passed exam or doctoral minimum in the specialty;
- Protocol of the Department Council for preliminary discussion of the doctoral thesis and the decision for the start of the procedure and for selection of the members of the scientific jury;
- The doctoral thesis;
- The author's summary;
- List of scientific publications on the subject of the dissertation;
- Copies of the scientific publications;

- List of participations in scientific forums;
- List of citations;
- Declaration of originality and authenticity of the attached documents;
- Other documents related to the course of the procedure.

The PhD student has presented 3 publications indexed and referenced in SCOPUS, of which one in a foreign journal, and has 4 participations with presentations in international forums and has participates in one scientific project.

Presentation of the PhD candidate

The PhD candidate Dolina Gencheva Gencheva has completed her secondary education at the English Language School Plovdiv, Plovdiv with an excellent academic record in 2008. In 2014 she completed her Higher Education in Medicine at Medical University - Plovdiv, with an excellent academic record, and the Award "Golden Hippocrates". In the period 2015 - 2019 she specialized Cardiology at Medical University – Plovdiv with practical base for specialization UMHAT "Sv. Georgi" Plovdiv, Clinic of Cardiology.

Clinical experience:

from 02.2015 to 02.2016 - Medical doctor at the Clinic of Cardiology, UMHAT "Sv. Georgi" Plovdiv

from 2015 to 2019 - Specialization of Cardiology at the Clinic of Cardiology, UMHAT "Sv. Georgi" Plovdiv

from 01.2017 and currently - Assistant prof. at the First Department of Internal diseases, section of Cardiology, Medical University – Plovdiv

from 06.2019 - Medical doctor, Cardiology, at the Clinic of Cardiology, UMHAT "Sv. Georgi" Plovdiv

from 16.12.2021 - PhD student, independent form, at the at the First Department of Internal diseases, section of Cardiology, Medical University – Plovdiv

Teaching experience:

✓ Practice classes in Cardiology of medical students, training in Bulgarian and English;

✓ Practice classes of trainee doctors during pregraduate internship in Cardiology;

✓ Lectures included in the main theoretical course for Cardiology residents at the First Department of Internal Medicine, Cardiology, Medical University – Plovdiv

✓ Presentation of a clinical case and moderation of scientific sessions within the international congress World Cardiology and Cardiologist Meeting 11-12 September 2018, under the "DOKTORANT-2" project

Scientific activity: The PhD student has presented 3 publications indexed and referenced in SCOPUS, of which one in a foreign journal, and has 4 participations with presentations in international forums and has participates in one scientific project.

2. Relevance of the topic

Hypertensive disorders of pregnancy are at present, still amongst the most common pathologies of pregnancy. On the other hand, the presence of hypertension and preeclampsia in a previous pregnancy is a major risk factor for their appearance in a subsequent one. In addition, these women are also at higher risk of developing cardiovascular disease and diabetes later in life. The investigation and demonstration of organic and functional changes of the heart during preeclampsia and gestational hypertension, and in this sense their importance as a risk factor for different cardiovascular pathologies after the pregnancy, could have an important clinical-applied benefit. This is one of the main merits of the current doctoral thesis.

3. Knowledge on the topic

The literature review is based on 278 publications, of which 8 in Cyrillic and 270 in Latin. This number of authors is a good prerequisite for a detailed acquaintance with the topic of the doctoral thesis. The review examines in details the theories of the occurrence, pathogenesis and clinical significance of hypertension and preeclampsia, as well as the guidelines for the prevention of cardiovascular disease, which cite hypertension in pregnant women and preeclampsia as one of the main risk factors. All this demonstrates a detailed and thorough knowledge of this interdisciplinary problem, and is a prerequisite for carrying out a competent study, and an objective credibility of the conclusions.

4. Methodology of the study

A prospective, single-center, clinic-epidemiological study was carried out in the period from 15.08.2018 until 15.01.2020. The study was conducted on the territory of two departments of Medical University - Plovdiv – the First Department of Internal diseases, section of Cardiology and the Department of Obstetrics and Gynecology. The study enrolled 123 pregnant women divided into three groups.

The information was collected by a questionnaire covering a sufficient quantity of the necessary factors corresponding to the study plan. Venous blood was taken from all patients on the day of the ultrasound examination.

The methods of investigation include:

Physical methods: Anamnesis, Physical status, Electrocardiogram, Echocardiographic examination

Laboratory methods:

There are two categories of laboratory methods:

1. Routine laboratory tests.
2. Tests to determine the levels of specific biomarkers.

Statistical methods for processing and analysis of the data obtained:

The data was entered into and processed with IBM SPSS Statistics 25.0 (IBM SPSS Statistics for Windows, SPSS Inc., Chicago, IL, USA) and MedCalc Version 14.8.1 (MedCalc Software,

Mariakerke, Belgium). $P < 0.05$ was accepted as a level of significance for rejecting the null hypothesis.

Fourteen statistical methods, tests and analyses were used, enabling the correct refinement and selection of data, which implies an adequate interpretation of the results and high statistical reliability of the conclusions.

5. Characteristics and evaluation of the doctoral thesis and its contributions

The doctoral thesis is of sufficient volume, consists of 197 standard print pages and is well illustrated with 24 figures, 66 tables and 3 supplements. The literature review is based on 278 publications, of which 8 in Cyrillic and 270 in Latin, well arranged in clearly defined sections, and provides an appropriate basis for a detailed and systematic study of the problem.

The analysis of the literature review is detailed and identifies the main directions in which the study is going. In it, the author introduces us to the structure and the clinical significance of hypertensive disorders of pregnancy in the world, presents the main changes in the cardiovascular system during pregnancy and their echographic evaluation and introduces us to the biomarkers included in the study. For this purpose, a sufficient number of large-scale studies, analyses and meta-analyses, directly and indirectly related to the topic, are examined and discussed. Also, as a natural transition to the core of the study, the author presents some unresolved and unclear issues.

The purpose of the study is clearly and accurately formulated. The assigned objectives allow for a good analysis of the structural and functional changes of the cardiovascular system in women with gestational hypertension and preeclampsia, as well as for predicting their future health, based on a combination of echographic parameters and biomarkers.

The study included 123 pregnant women at the mean age of $29,93 \pm 5,71$ years, ranging from 18-43 years, divided into 3 groups:

- Group 1 (women with gestational hypertension) – 36 (29,3%);
- Group 2 (women with preeclampsia) – 37 (30,1%);
- Control group – 50 (40,7%).

The inclusion and exclusion criteria are carefully and correctly selected.

The factors and parameters for comparison between the three groups are introduced comprehensively in sufficient details.

The results are presented in a consistent and systematic way, well-illustrated by figures and tables. The specified parameters and factors are sufficient.

The assumption that the PhD candidate makes as a conclusion, when discussing the general characteristics of the women, **that there would be some benefits for Obstetrics and Gynecological practice in including a family history for arterial hypertension as a regular question in the anamnesis of women in early pregnancy**, is correct. Such a "positive" history should be considered in the assessment of pregnancy as potentially risky and should be associated with a stricter follow-up.

The fact that Bulgarian women are in the top of women smoking during pregnancy in the world is alarming. Ignoring the many negative effects of this harmful habit, especially for pregnant women, is really a sign of a low level of health-consciousness and awareness.

The section "Associations" forms the foundations of the Doctoral thesis, on which the most of the conclusions, deductions and contributions are based. It is noticeable that LV GLS values are not significantly affected by the values of hemoglobin, amount of protein in urine, total protein and albumin in serum, uric acid, parity, maximum measured systolic or diastolic pressure, the gestational age at which elevated blood pressure was first registered, as well as the time from the first detection of the elevated blood pressure till the inclusion in the study. This makes it possible to identify the statistically reliable factors determining the risk of abnormal LV GLS occurrence: preeclampsia, gestational hypertension, and current BMI ≥ 28 kg/m².

Additionally, in the conclusions of the section "Associations" there is an interesting assumption that it is possible some biomarkers for cardiovascular pathology to also carry information about the impact of hypertensive disorders on the fetus and be potentially used to predict the outcome of pregnancy.

The conclusions are 8 in number, clearly formulated, and in synthesized form reflect the analyzed results. The discovery of credible changes in the echographically assessed structure and function of the heart practically fulfills the original purpose of the doctoral work. It is necessary to pay attention to the fact that nearly half of the women with a risk profile for developing preeclampsia and gestational hypertension are smokers or have an unfavorable BMI. Unfortunately, the majority of women today find it normal to smoke during their pregnancy and to have an inappropriate diet. Results similar to those made by Dr. Gencheva should receive public awareness for health educational purposes!

Proving that preeclampsia, gestational hypertension and BMI ≥ 28 kg/m² are independent predictors of the occurrence of abnormal LV GLS is another merit of the doctoral thesis.

Conclusion N 8 shows some very interesting correlations, such as between high PIGF values and less pronounced echographic changes. Also, that with preeclampsia, higher NT-proBNP values correspond to better indicators of left ventricular systolic (GLS) and diastolic function. These are conclusions that could have clinical and prognostic value.

Contributions of the doctoral thesis

The doctoral thesis of Dr. Dolina Gencheva has scientific and theoretical contributions as well as contributions of a confirmatory and applied nature.

Contributions of a primarily scientific and theoretical nature:

1. Original contribution for Bulgaria is the identification of echocardiographic parameters applied in clinical practice, which detect differences between groups with gestational hypertension, preeclampsia and normotensive pregnant women.

2. For the first time in Bulgaria, the discriminatory abilities of the listed five biomarkers for distinguishing between pregnant patients with gestational hypertension and preeclampsia, and healthy normotensive pregnant women were studied.

3. A comprehensive analysis was carried out and associations were established between the echocardiographic parameters and the five biomarkers in pregnant women with gestational hypertension, preeclampsia and normotensive pregnancies.

Contributions of a primarily applied nature

1. An input document for the generation of a database and a database "Pregnant women with gestational hypertension/preeclampsia" were created.

2. The study encompassed a young population with an early, gender-specific risk factor for cardiovascular events, allowing for a further follow-up and control of other risk factors for the purpose of primary prevention.

3. The global longitudinal strain, based on speckle tracking, has been proven as a more sensitive modality for the detection of changes in the systolic function of both ventricles in this population, compared to the classically measured parameters.

4. Based on the observed differences in the echocardiographic parameters and biomarker levels, models for the evaluation and prediction of cardiovascular risk in such populations can be subsequently created.

6. Assessment of the publications and personal contribution of the PhD student

The PhD candidate has presented 3 publications in journals referenced in the SCOPUS database, has 4 participations with presentations in national and international forums and participates in one scientific project, all related directly to the topic of thesis. The PhD candidate herself collected and processed the data of the patients enrolled in the study.

Critical remarks:

I have no critical remarks.

Recommendations:

1. Developing an algorithm with a predictive value always has a clinical significance. Future scientific work may continue in this direction.

7. Author's summary

The author's summary meets the requirements for volume, structure and conveniently and in an easily accessible way presents the content of the main results, conclusions and deductions of the dissertation in a synthesized form.

CONCLUSION

The doctoral thesis contains scientific and applied results, which represent an original contribution to science and meet all the requirements of the Law on Development of Academic Staff in the Republic of Bulgaria, the Regulations for Implementation of the Law and the Regulations of Medical University - Plovdiv. The presented materials and dissertation results are fully in line with the specific requirements adopted in connection with the Regulations of the Medical University – Plovdiv for the application of the Law on Development of Academic Staff in the Republic of Bulgaria.

The doctoral thesis shows that the PhD candidate Dolina Gencheva Gencheva possesses deep theoretical knowledge and professional skills in the scientific specialty "Cardiology", demonstrating qualities and skills for independent scientific research.

In view of the above, I am confidently giving my positive assessment of the study presented by the doctoral thesis reviewed above, the author's summary, achieved results and contributions, and I propose to the honorable scientific jury to award the educational and scientific degree "Doctor of Philosophy" to Dr. Dolina Gencheva Gencheva in the Doctoral Program "Cardiology".

29.09.2021 r.

Author of the review:

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