

STATEMENT

Regarding the doctoral thesis for obtaining the educational and scientific degree Doctor of Philosophy on the topic „**Assessment of changes in cardiac structure and function in pregnant women with preeclampsia and gestational hypertension**”

Author of the doctoral thesis:

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Prof. Arman Shnork Postadzhiyan, MD, PhD, UMHAT “Sveta Anna”, Medical University – Sofia, member of the scientific jury, appointed by the order of the Rector of Medical University - Plovdiv

The following statement is written in accordance with the Law for Academic staff development and its regulations and the Regulations and the Procedure of obtaining scientific degrees and academic positions of Medical University – Plovdiv.

The presented set of materials in paper/electronic form is in accordance with the procedure for acquiring the scientific and educational degree Doctor of Philosophy and the Regulations of the Medical University - Plovdiv. I did not discover plagiarism during the review process of the provided thesis, author's summary or publications related to the thesis development.

I declare a lack of common scientific research with the PhD candidate or a potential conflict of interest.

According to the World Health Organization, hypertension is the most common complication of pregnancy in the modern world. About 4-10% of all pregnant women are affected. There is evidence of a higher risk for the development of arterial hypertension, ischemic heart disease, cerebrovascular disease, diabetes, venous thromboembolism, and even a higher cardiovascular mortality in women with hypertensive disorders of pregnancy. This risk is increased in the first few years after the pregnancy and also at a later age. However, the role of hypertensive

disorders of pregnancy as a long-term risk factor is often overlooked and post-pregnancy follow-up is not usually performed. In a significant number of studies of women with preeclampsia and gestational hypertension, abnormalities in the cardiac structure and function have been identified, which are expressed to varying degrees - as assessed echocardiographically and with the use of various biomarkers. The registered changes are usually asymptomatic, but they, similarly to the high blood pressure, can persist for some time after the end of pregnancy and recur in subsequent pregnancies.

This is the background that motivated Dr. Gencheva to choose the topic "Assessment of changes in cardiac structure and function in pregnant women with preeclampsia and gestational hypertension".

Structure of the doctoral thesis:

Dr. Gencheva's dissertation is written on 197 standard pages, of which:

- 1. Title page – 1**
- 2. Content - 1**
- 3. Acronyms – 2**
- 4. Literature overview - 36**
- 5. Aim, objectives – 1**
- 6. Materials and methods - 17**
- 7. Results – 74**
- 8. Discussion - 36**
- 9. Conclusions and contributions – 3**
- 10. Supplements - 3**
- 11. References – 13**

The ratio literature overview/methods/results-discussion is optimal, respectively 35:10:55%. The dissertation contains a total of 24 figures, 66 tables and three supplements. The reference list consists of 278 sources, of which 8 in Cyrillic and 270 in Latin. The majority of the cited articles are directly related to the research topic.

In connection with the dissertation work, three scientific articles were published in journals that are indexed and referenced in international databases, with fragments of the dissertation work reported at 4 national and international forums. Dr. Gencheva has participated as a chief investigator in a project funded by Medical University - Plovdiv, as well as in the international project „DOKTORANT 2”. Based on the abovementioned, the publication activity of the PhD student is optimal and meets the criteria for obtaining the scientific and educational degree Doctor of Philosophy.

Characteristic features of doctoral thesis:

The topic of the dissertation "Assessment of changes in cardiac structure and function in pregnant women with preeclampsia and gestational hypertension" is appropriately selected in terms of significance of the problem, current relevance and future possibilities. In essence, a large-scale epidemiological and clinic-instrumental and laboratory study was conducted to answer the question of whether the presence of preeclampsia and gestational hypertension had had an impact on certain echocardiographic parameters and biomarkers associated with heart structure and function and to what extent. This could improve the follow-up of women, both during the pregnancy and after, and predict the existence of an increased risk of cardiovascular disease in some of the women in the longer term.

Patient data were collected prospectively in the period from 15.08.2018. until 15.01.2020, at two of the departments of the Medical University - Plovdiv - First Department of Internal Diseases. section of Cardiology and the Department of Obstetrics and Gynecology. This is the first in Bulgaria more in-depth study to investigate the characteristics of preeclampsia and gestational hypertension, in which modern echocardiographic methods and biomarkers are used to establish associations and the potential prognostic significance that some of them would have in the long term.

The literature overview, as far as systematic and analytical qualities of examining the available information are concerned, represents the PhD student as a leading expert on the problem. The importance of hypertensive disorders of pregnancy, the pathogenesis of preeclampsia and risk factors, cardiovascular risk in preeclampsia and gestational hypertension, and the guidelines are consistently covered.

Changes in the cardiovascular system of the mother during pregnancy were examined, with the main focus put on their echocardiographic evaluation and biomarkers in preeclampsia and gestational hypertension. At the end of the literature review, the data are systematized, which makes a good impression. The scientific ground of the study is established at the end of the review in the form of conclusions.

The aim of the doctoral thesis is clearly formulated – To determine the changes in the cardiac structure and function of women with preeclampsia and with gestational hypertension in order to improve the evaluation and the prognosis of the conditions.

The following objectives are listed:

1. To analyze data on patients with preeclampsia, gestational hypertension and healthy pregnant women concerning anamnesis, including obstetric anamnesis, risk factors and family history for cardiovascular disease, physical status, laboratory tests.

2. To analyze echocardiographic parameters giving information on cardiac morphology, systolic and diastolic function in women with preeclampsia and gestational hypertension and to compare them with those in healthy pregnancies.

3. To determine the serum concentration of certain biomarkers (NT-proBNP, Galectin-3, hs-CRP, IL-6 and PIGF) for cardiac, endothelial and placental dysfunction in women with the studied pathologies and compare to those in healthy pregnant controls.

4. To determine whether there are associations between:

4.1 Some echocardiographic parameters (global longitudinal strain of the left ventricle) and certain characteristics of the women (as set out in point 1);

4.2. The biomarkers and certain characteristics of the women;

4.3. The echocardiographic parameters and the biomarkers.

The methodology of the study with regard to the non-invasive and the established definitions is appropriate for the reliability and the credibility of the reported results and includes clinical (anamnesis and physical examination), instrumental, laboratory and statistical methods of examination.

The chief method of investigation was transthoracic echocardiography, which was done according to the instructions for image recording and calculation of parameters, stated in the current echocardiography guidelines, endorsed by the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). Multiple parameters of left ventricular systolic (LV) and diastolic function, global longitudinal strain of the LV (LV GLS), left atrium and right heart involvement in the pathological process were analyzed. The dimensions for which indexing is recommended in the guidelines

were indexed according to body surface area. Besides routine laboratory tests, the concentrations of following biomarkers were also determined: Galectin-3, Interleukin-6, hs-CRP, PIGF, NT-proBNP.

The results are convincing and presented clearly and accurately — for the whole study group and as well as by subgroups, enabling the data to be tracked and compared. Appropriate statistical methods were used to obtain the results.

The main **results** of Dr. Gencheva's thesis can be summarized as follows:

1. In the study group a strong correlation between BMI and BSA is present, and therefore indexing of echocardiographic parameters according to BSA is recommended in order to avoid the influence of BMI, which is typically higher in hypertensive disorders of pregnancy

2. The gestational hypertension group had more echocardiographic parameters being statistically equal to those in the preeclampsia group, than to the controls. There was no significant

difference between the two hypertensive groups regarding the left ventricular GLS, as well as for the majority of diastolic functional parameters.

3. Structural or functional cardiac changes were not present in all of the women with a hypertensive pathology. At the same time, not all women with preeclampsia or gestational hypertension will develop cardiovascular diseases, despite having a higher risk. The results of this study enable us to make a more precise risk assessment within the pathological groups, and thus to pay special attention to the women with the most pronounced changes.

4. Regarding the left-chamber parameters: a significant difference was present only in the indexed volume of left atrium between the hypertensive and the normotensive pregnant women; there was a more pronounced left ventricular hypertrophy and remodeling in hypertensive pregnancies; and for the mixed pathological group concentric remodeling was the most common left ventricular geometry pattern; There were significant differences in multiple parameters of systolic and diastolic left ventricular function between women with hypertensive and normotensive pregnancy, evidencing a more impaired left ventricular function in the studied pathologies;

5. Regarding the right-chamber parameters: a significant difference was observed for the mean values of the indexed volume of the right atrium between the preeclampsia and the gestational hypertension group, and there were also significantly higher means for the proximal and distal diameters of the right ventricular outflow tract for both of the pathological groups compared to the normotensive pregnant women; there were significant differences in the parameters of systolic and diastolic right ventricular function between the women with hypertensive versus those with normotensive pregnancies, again with evidence of a more impaired right ventricular function in the pathologies;

6. For the majority of the echocardiographic parameters and biomarkers - PIGF, Galectin-3, Interleukin-6 and hs-CRP, the women with gestational hypertension showed no statistical difference from those with preeclampsia, which leads to the interpretation that the lack of registered proteinuria likely does not equal a more favorable cardiovascular reaction to the hypertensive pregnancy.

7. NT-proBNP levels were higher in preeclampsia compared to gestational hypertension, while hs-CRP levels were higher when comparing gestational hypertension with the controls, but not preeclampsia with the controls, which may suggest differences in the underlying pathophysiologic mechanisms.

8. The correlation analysis gave the following results: PIGF had the greatest number of correlations with the echocardiographic parameters, with higher values corresponding to less pronounced changes; Isolated for the preeclampsia group, higher NT-proBNP values corresponded to better indicators of left ventricular systolic (GLS) and diastolic function; For the rest of the

biomarkers, higher values mostly corresponded to more pronounced structural and functional changes.

The summary corresponds to the results and the same applies to the conclusions that are established. The dissertation's contributions are of a pronounced scientific and applied nature, well formulated and are the result of the study.

I believe that the topic addressed by the PhD candidate is among the important issues of modern hypertensiology and cardiology and deserves to be enriched and expanded in the future. By its nature, this is one of the first for our country studies to more systematically report results by creating a database "Pregnant women with gestational hypertension/preeclampsia". A young population with an early, sex-specific risk factor for cardiovascular events is encompassed, allowing for its further follow-up and control of other risk factors for the purpose of primary prevention. Based on the observations of echocardiographic and biomarker differences, models for the precision and prediction of cardiovascular risk in such populations can be subsequently built.

I am convinced that the topic of dissertation and the amount of work done significantly exceeds the legal requirements for successful defense of a PhD thesis. I particularly commend the successful attempt to systematize and present the data with the most appropriate statistical methods, as well as the summary of the data at the end of each chapter.

In conclusion, the dissertation presented by Dr. Dolina Gencheva Gencheva contains scientific, scientific and applied and applied results that represent an original contribution to science and meet the requirements for awarding the educational and scientific degree Doctor of Philosophy. The dissertation thesis shows that the PhD candidate possesses in-depth theoretical knowledge and professional skills in the scientific specialty, demonstrating qualities and skills for conducting and discussing scientific research independently.

On these grounds, I vote positively and propose to the honorable members of the Scientific Jury to vote positively and propose to the Rector of the Medical University - Plovdiv to award the scientific and educational degree PhD under the Doctoral Program Cardiology to Dr. Dolina Gencheva Gencheva.

15.09.2021

Prof. Arman Shnorik Postadzhiyan, MD, PhD,
Medical University - Sofia

