

REVIEW

By Prof. Plamen Marinov Gatsov, M.D., DSc

Scientific Institute of Medical University - Pleven

of a Doctoral Thesis for obtaining the educational and scientific
degree "Doctor of Philosophy"

Scientific specialty: Cardiology (code 03.01.47)

**Topic: „Assessment of changes in cardiac structure and function in
pregnant women with preeclampsia and gestational hypertension”**

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In accordance with order № P-1185/19.07.2021 by the Rector of Medical
University – Plovdiv, Prof. Mariana Atanasova Murdzheva, M.D., PhD, M.H.M.

1. Relevance of the topic

Arterial hypertension (AH) is an especially important problem in modern medicine. It is the most common chronic disease in the elderly in the countries of Europe and North America. As the age of pregnancy and childbirth increases in women from the same regions, the likelihood of a combination of pregnancy and arterial hypertension is also increasing. Gestational hypertension (GH) and preeclampsia (PE) are the most common forms of hypertensive disorders in pregnant women. Their presence leads to a significantly higher rate of complications during pregnancy for both the mother and the fetus. For the

mother, these are eclampsia, premature birth, cerebral hemorrhage, renal and hepatic failure, HELLP syndrome, and for the fetus – growth retardation. Despite the progress of modern medicine, these conditions continue to be an essential threat to the health and life of the pregnant woman and child.

Dr. Gencheva's doctoral thesis sets the important task, with the help of modern clinical, instrumental and laboratory methods to detect early changes in the cardiac function of women with gestational hypertension and preeclampsia, in order to provide a more accurate diagnosis and assess the prognosis.

2. Structure of the doctoral thesis

The doctoral thesis of Dr. Gencheva consists of 197 pages. It is illustrated by 24 figures and 66 tables. There are 3 supplements. The references included 278 articles, 8 of which in Cyrillic and 270 in Latin.

a) literature review

The overview is presented on 36 pages, structured in 5 subsections dealing with the definitions and significance of hypertensive disorders of pregnancy; theories for their pathogenesis and risk factors for preeclampsia; the cardiovascular risk in gestational hypertension and preeclampsia; the guidelines for gestational hypertension, preeclampsia and cardiovascular diseases; cardiovascular changes in the maternal organism during pregnancy and echocardiographic evaluation, as well as the role of a particular group of biomarkers in the diagnosis follow-up of pregnant women with gestational hypertension and preeclampsia.

The last subsection covers the unresolved, according to the PhD candidate, problems, namely: insufficient studies of gestational hypertension in scientific literature, critique of proteinuria as a factor defining preeclampsia, the small number of studies using both echocardiography and biomarkers in these pregnant women as the utilization of this combination of parameters can further

stratify the risk in those subgroups of women, thus defining the "target groups" for more active monitoring and treatment.

b) Aim and objectives

The aim 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."

In order to achieve the aim, the PhD student has set 4 appropriate objectives, the last of which with 3 subtasks.

c) methods

For the period from 15.08.2018 to 15.01.2020 in a prospective one-center, clinico-epidemiological study, Dr. Gencheva examined a population of 123 women hospitalized at the Clinic of Obstetrics and Gynecology of UMHAT "Sv. Georgi" Plovdiv, or referred by outpatient Obstetrics and Gynecology specialists. The participants were selected in accordance with extensive inclusion and exclusion criteria.

The examined pregnant women were separated into 3 categories:

1. Gestational hypertension - 36
2. Preeclampsia - 37
3. Normotensive controls – 50

The mean age of the participants in the study was 29.93 ± 5.71 years.

The patients were examined using detailed questionnaires, taking of physical status, ECG, echocardiography and laboratory tests. Echocardiographic examination is extremely detailed and includes a very thorough set of indicators reflecting the morphological and functional characteristics of the participant's heart. Laboratory studies include both routine ones and tests to determine the levels of specific

biomarkers such as NT-ProBNP, Galectin-3, high-sensitivity C-reactive protein, interleukin-6 and placental growth factor (PIGF).

The collected data is analyzed with a great number of statistical methods.

3. Results and discussion

Comparing between the pathological groups and between them and the controls, Dr. Gencheva found important associations between the presence of GH and PE and a number of factors such as number of pregnancies (hypertensive disorders being more common in first pregnancy), hypertensive disorder in a previous pregnancy, body mass index, family history of arterial hypertension and the presence of GH or PE in close relatives. Women with GH and PE had significantly higher body mass index before and during pregnancy compared to the controls.

From the echocardiographic study, an association is found between the presence of GH, PE and a number of parameters such as dimensions and volumes of the left atrium, the left ventricle (LV), wall thickness of the LV, dimensions of the right atrium, the right ventricle, etc. However, indexing a large number of these parameters to body surface area leads to the disappearance of the differences between the groups. The LV mass index also differs between the groups. There is deterioration in the parameters of LV diastolic function, and modern methods, such as tissue Doppler can detect these changes much earlier.

For the right heart chambers, significant differences were also found between the groups as far as the dimensions of the right atrium, the right ventricle, as well as the systolic and diastolic function of the right ventricle, assessed with tissue Doppler, were concerned. The correlation analysis carried out does not prove a relationship between the echographic parameter LV GLS and the height and weight of the newborn.

With regard to the biomarkers studied, the presence of levels below the cut-off value for PIGF was significantly related to the presence of GH and PE. Galectin-3 and IL-6 had statistically higher values in the pathological groups compared to the controls. The GH group had significantly higher hs-CRP values, and the two pathological groups had significantly lower PIGF values than the controls. The PE group and controls had significantly higher NT-proBNP values than those with GH. The possible correlations between the anamnestic, physical exam and the echocardiographic parameters and the biomarkers were carefully studied for each group.

A thorough discussion of the results is presented and consists of 38 pages.

4. Conclusions and contributions

The conclusions are formulated in 8 points, the last one with 3 sub-points. They can be summarized as follows: pregnant women with GH and PE have a less favorable cardiovascular profile; changes in echocardiographically-established heart structure and function are more common; novel echocardiographic parameters, such as two-dimensional global longitudinal strain are more sensitive than the classical one for the detection of early functional changes in pregnant women; according to the parameters studied, women with GH showed great similarities to those with PE, which according to Dr. Gencheva, makes the classic distinction – proteinuria, less significant; differences in the NT-proBNP and hs-CRP levels between the women with GH and PE may suggest a difference in the underlying pathophysiological mechanisms; GH, PE and an increased body mass index of ≥ 28 kg/m² are all independent predictors of abnormal LV GLS; PIGF is the marker with the most correlations with the echocardiographic parameters; in the PE group, higher NT-proBNP levels corresponded to a better systolic and diastolic function of the LV, while the higher values of the other biomarkers corresponded to more pronounced structural and functional changes.

The contributions are 7 in total and are divided by the PhD candidate into 3 with a predominantly scientific and theoretical original character and 4 with a predominantly applied character. Of the former kind is the identification for the first time in Bulgaria of echocardiographic and biomarker parameters, which individually and in combination can distinguish pregnant women with GH or PE from those with normal pregnancy and between the pathologies themselves. Of the second kind are the creation of an entry document for the generation of a database for research of pregnant women with GH and PE; encompassing a young population with an early risk profile for the development of cardiovascular diseases, allowing for primary prevention, as well as the possibility, on the basis of the identified echocardiographic differences between the studied groups, to build models for the precision and prognosis of the cardiovascular risk in such populations.

5. Some remarks

I accept the conclusion on page 64 that GH and PE are more common in first pregnancy, but on the condition that there is the likelihood that women who have had these disorders are less likely to become pregnant again due to subjective reasons. Thus, the sample cannot be considered representative for this indicator. However, this conclusion was not considered a major one by the PhD candidate and was not specifically written at the end of the dissertation work.

I have no other remarks for the PhD candidate.

6. Publications, related to the doctoral thesis

Dr. Dolina Gencheva has presented 3 full-text publications in referenced and indexed journals, related to her doctoral thesis, one of which is still in-press and a document for upcoming publication is attached. She has also presented 4 scientific reports: 3 in Bulgarian and 1 at an international forum.

7. Conclusion

The doctoral thesis of Dr. Dolina Gencheva is relevant and of significant social importance. Care for pregnant women, early detection of pathological deviations during the course of pregnancy, their prevention and treatment are of great importance. The PhD candidate conducted a thorough prospective study of pregnant women with GH and PE. She utilized a wide range of clinical, instrumental and laboratory parameters to characterize pathological abnormalities in these pregnant women and compared them with a control group of women with normal pregnancies. The results are presented logically and in detail, and the conclusions and contributions are clearly formulated. I believe that the thesis presented by Dr. D. Gencheva fulfils all the criteria for the acquisition of the educational and scientific degree "Doctor of Philosophy" in the scientific specialty of Cardiology. I strongly recommend to the esteemed Scientific Jury to award this degree to Dr. Dolina Gencheva, for which I also give my positive vote.

05.10.2021

Sincerely: 

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