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PhD THESIS

THE ROLE OF THE BIO-MARKER CA-125 IN HYPERTENSIVE DISORDERS OF PREGNANCY

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The current doctoral thesis includes a general, theoretical part and a special part, composed of two distinct original articles, previously published in specialized scientific journals. The theoretical part focuses on the collection and integration of relevant data available in the literature, in order to adequately characterize the contemporary context, respectively the scientific motivation, for further research, included in the special part, that documents the role of the CA-125 biomarker in the hypertensive disorders of pregnancy.

In order to achieve the proposed objectives, a comprehensive review of the current knowledge on the subject addressed was elaborated, including, elements of epidemiology, the clinical definition of the forms of hypertensive disorders of pregnancy, the classification of hypertensive disorders of pregnancy, the etiopathogenic mechanism of hypertensive disorders of pregnancy and elements of prevention. Also, the current methods used in the screening of hypertensive pregnancy pathology are presented, identifying at the same time the disadvantages of the existing strategies in clinical practice. The last chapter in this part addresses the biomarker CA-125, presenting the pathophysiology of this marker, as well as the current knowledge regarding its use as a tumor marker, a marker of heart failure and last but not least in the hypertensive disorders of pregnancy.

Afterwards, the special part addresses the research topic outlined in the general part, by investigating the CA-125 biomarker in the main contexts of clinical utility highlighted, in order to evaluate its potential in the management of hypertensive disorders of pregnancy.

The investigation of the CA-125 biomarker allowed the development and publication of two original articles. Therefore, the current thesis evaluates the role of CA-125 as a marker in the management of severe pre-eclampsia as well as the potential role of CA-125 in the first trimester screening of pre-eclampsia.

The study population of the current thesis includes two series of pregnant patients who presented in the ambulatory or continuous hospitalization system for prenatal care in the Obstetrics-Gynecology clinics of Timișoara Municipal

Emergency Clinical Hospital between January 2022 and June 2022 , respectively January 2022 – January 2023.

The first study included the first series of patients, totaling a number of 100 pregnant women with a gestational age over 25 weeks as the main inclusion criterion. This batch was divided into 2 main groups. The first included 50 patients with elevated blood pressure values at the time of inclusion in the study, while the second group represented the control group including 50 patients with normal blood pressure values at the time of inclusion and also, who were not diagnosed with a form of pregnancy-induced hypertension up to the time of birth. Patients who did not accept full pregnancy monitoring from the time of inclusion in the study, patients who could not provide the clinical data from the current pregnancy that were proposed for analysis in the research design, as well as pregnant women with a history of chronic essential hypertension, known kidney or liver disease, diabetes mellitus, known ovarian or uterine gynecological pathology, multiple pregnancy, known fetal abnormality and/or pregnancy obtained through an assisted reproductive technique were excluded from the recruitment. The group of hypertensive pregnant women was later subdivided according to ACOG (American College of Obstetricians and Gynecologists) criteria into the subgroups of gestational hypertension, non-severe pre-eclampsia and severe pre-eclampsia, obtaining subgroups of 22, 11, and 17 patients, respectively. Using the blood pressure values, mean blood pressure was calculated according to the formula MAP = DP + 1/3(SP – DP).

For each pregnant woman included in the group, a series of socio-demographic parameters (age, parity, smoking), clinical (gestational age, mean blood pressure, obstetric history, aspirin treatment), and ultrasound (pulsatility index of uterine arteries from the first and/or second trimester) were collected from the history of the current pregnancy. Serum and urine biological samples were also collected according to the standard for evaluating pregnant women with hypertensive disorders of pregnancy recommended in the national guidelines: proteinuria per 24h, platelets, transaminases, serum creatinine and

also lactate dehydrogenase (LDH). Last but not least, the CA-125 marker was collected and dosed using the ECLIA method according to the standards of the external laboratory where it was processed. All pregnancies were followed until birth, information on the presence of intrauterine fetal growth restriction, gestational age at birth, birth weight of the newborn, APGAR score at birth, respectively the need for care in the Neonatal Intensive Care Unit of the newborns being collected from the SCMUT database.

Following the descriptive analysis of the collected data, the enrolled group had an average age of 29 years with a parity that varied between 1 and 4 births. Also, the average gestational age at enrollment was 34.4 weeks of gestation. No statistically significant differences were observed in terms of the characteristics of the study population in the 2 groups, respectively with the 3 subgroups. From the point of view of the history of enrolled pregnant women, 11% had a history of hypertensive disorders in previous pregnancies, predominating in the group of patients with hypertension in the current pregnancy; 13% were following a prophylactic treatment with low-dose aspirin; 16% were smokers.

Mean arterial pressure showed statistically significant differences between the normotensive group and all subgroups with hypertension and also between the group with gestational hypertension and severe pre-eclampsia.

The comparison of the mean values of the determined biological parameters showed significant differences between the subgroups in terms of proteinuria over 24 h, platelet count and lactate dehydrogenase. Analysis of CA-125 marker values showed progressively increasing mean values, from a value of 8.97 U/ml for the normotensive group to 21.23 U/ml for the group with severe pre-eclampsia. Statistically significant differences were observed between the normotensive group and the hypertensive group as well as between the group with severe pre-eclampsia and gestational hypertension.

When analyzing the parameters related to the evolution of pregnancies, a significantly lower gestational age at birth was observed for the subgroups of

pregnant women with pre-eclampsia compared to normotensive ones, as well as a lower birth weight. There were no significant differences in relation to the APGAR score at birth. Also, a significant difference was observed between mean CA-125 values between neonates who required care in NICU and those who did not required. Another interesting aspect was the statistically significant difference between the mean value of CA-125 in mothers with fetuses affected by IUGR versus those with fetuses of normal weight for gestational age.

Pearson regression tests were applied to parameters to test for correlation. The following significant relationships were observed between CA-125 value and biological and clinical parameters: a positive correlation with mean blood pressure, 24h proteinuria and LDH and a negative correlation with platelet count, gestational age and birth weight.

For diagnostic performance testing, a cut-off value was calculated using an ROC curve. Thus, the best predictive value for severe pre-eclampsia, with a sensitivity of 64.71% and a specificity of 81.82% with a negative predictive value of 81.8% was 19.8 U//ml.

In the second study, involving the second series of pregnant patients, the main inclusion criterion was gestational age between 11+0/7 weeks and 14+0/7 weeks. Other inclusion and exclusion criteria were similar to the first study, emphasizing the need for patients to accept full prenatal monitoring from the time of inclusion. 50 pregnant patients were recruited.

The collected parameters included socio-economic data (age, parity, smoking), clinical (gestational age, obstetric history, aspirin treatment, blood pressure), paraclinical (uterine artery pulsatility index – UtA-PI) and biological (PAPP- A). Mean arterial pressure (MAP) was calculated for each patient according to the formula MAP = DP + 1/3(SP – DP). Likewise, MAP, PAPP-A, UtA-PI values were converted into multiples of median. For each patient, we measured the value of the CA-125 marker by processing with the ECLIA method according to the standards of the external laboratory used.

All patients were followed until delivery. Data were collected including blood pressure value (in the third trimester), gestational age at birth, newborn weight at birth and APGAR score at birth.

The average age of the included group was 29.3 years with a parity between 0 and 3 births. Gestational age at recruitment was 12.3 weeks of gestation. From the data collected from the patients' history, it was observed that 4% of the group had a history of hypertensive disorders of pregnancy in the previous pregnancies, 9% were smokers and 20% of the patients were taking low-dose aspirin treatment at the time of recruitment.

The mean values of the collected clinical parameters were a MAP of 86.3 mmHg or 1.01 MoM, a PAPP-A of 3.19 U/L or 1.41 MoM, 12% of patients having a pathological value (< 0.4 MoM). The mean UtA-PI was 1.18 MoM. The average value of CA-125 in the studied group was 20.2 IU/ml.

Correlation tests were applied to the parameters against the CA-125 value, observing a positive correlation only with the PAPP-A values of the first trimester.

In the third trimester, 12% of the included patients presented elevated blood pressure values being diagnosed according to the ACOG criteria with gestational hypertension in 5 cases and non-severe pre-eclampsia in one case. The mean MAP between the normotensive and hypertensive groups showed a significant difference (96 mmHg vs. 113 mmHg, $p<0.001$). The mean gestational age at birth was 38.3 weeks of gestation, and the mean weight of the newborns was 3223 grams. There were no significant differences in terms of these parameters between the normotensive and hypertensive groups.

Correlation tests were applied to third trimester parameters and first trimester CA-125 values, but no correlation was observed. The difference between the mean value of CA-125 between the normotensive group in the third trimester and the hypertensive group in the third trimester was also analyzed, but no statistical difference was observed (16.6 U/ml vs. 20.7 U/ml, $p=0.34$).

The current research materialized through the two original published articles aimed to evaluate the usefulness of the CA-125 marker in a different context. Little researched in the current literature but with sufficient evidence to support the scientific motivation of the current thesis. The obtained results provide promising medical evidence for its use in the management of hypertensive disorders of pregnancy, especially as an additional paraclinical parameter to the current criteria used in critical moments such as the decision to extract the fetus or hospitalize the hypertensive pregnant woman. Furthermore, through its wide availability and low-costs, its use has the potential to improve the management of these patients in resource-limited areas, areas where hypertensive disorders of pregnancy remains a major problem. This research is the first to include a Caucasian population, and it is also the first to address issues such as the analysis of the relationship with ultrasound parameters and especially with aspects of fetal outcomes such as intrauterine growth restriction or perinatal status. Unfortunately, the first trimester results rule out the potential of the marker as a screening parameter. However, the main limitation of the current research is represented by the numerically reduced study populations, due in particular to the difficulties of recruitment from the public hospital settings, thus suggesting caution in the use of published results and the need for further studies.

In conclusion, beyond the recognized limitations of the current thesis, the evidence reported by our research provides an interesting and potentially useful new direction for the CA-125 biomarker in the broad field of modern obstetrics, opening and encouraging promising clinical applications that could improve various aspects of the management of the hypertensive pathology of pregnancy.