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DOCTORAL THESIS

EFFECTS OF CARDIOVASCULAR RISK FACTORS AND HYPERTENSIVE DISORDERS ARISING DURING PREGNANCY ON THE BIOLOGICAL STATUS OF OBSTETRIC PATIENTS AND THE PRODUCT OF CONCEPTION

– A B S T R A C T –

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I. INTRODUCTION

The study was conducted in an era where humanity faces an increasing prevalence of cardiovascular diseases (CVD) among women of reproductive age. With the rise of obesity, diabetes (DM), and other comorbidities in society, cardiovascular pathologies have become a major public health issue and have direct implications on the health of pregnant women and the product of conception.

The historical context of our research finds its roots in the numerous studies that over the years have explored the relationship between the mother's health and neonatal outcomes. This has been a concern for the scientific community for decades but has received heightened attention in recent years as we better understand the complexity of the interaction between the maternal environment and fetal development.

Geographically, the research focuses on the pregnant women population in Romania, a country where CVD is the leading cause of death. However, our findings have global relevance, as the issue of cardiovascular pathologies during pregnancy is universal and affects women worldwide.

From a professional standpoint, this work is situated at the intersection of multiple disciplines, including obstetrics, cardiology, neonatology, and public health. Our research is of interest to doctors, nurses, researchers, and policy-makers working in these fields and who are concerned with improving the health of mothers and newborns.

As medical practice continues to evolve, understanding the complexities and dynamics between maternal health and newborn health becomes increasingly important. My fascination with the close and intricate connection between a mother's cardiovascular health and neonatal outcomes led me to delve deeper into this issue.

The cardiovascular health of the mother can profoundly impact neonatal health, with potential long-term effects on the child's health. As the incidence of CVD increases among the reproductive-age population, understanding these connections becomes even more urgent and relevant.

The proposed topic aligns with current concerns at the international, national, and regional levels regarding maternal and child health. It also aligns with our research team's interests, focusing on understanding how maternal illnesses can affect child health.

The main objectives of this research are: to analyze the relationship between cardiovascular risk factors (CRF), hypertensive disorders occurring during pregnancy, and the biological status of obstetric patients and the product of conception; to identify the

consequences of these pathologies on neonatal outcomes and develop intervention and prevention strategies that can improve both the mother's health and that of the newborn.

This work is structured into several main sections, including a comprehensive literature review, a detailed description of the methodology and theoretical frameworks used, a presentation of the obtained results, and a discussion on these results in the context of existing knowledge.

II. GENERAL SECTION

Pregnancy is a unique period in a woman's life, characterized by numerous physiological changes to ensure the optimal development and growth of the fetus. Among these changes, the cardiovascular system plays a central role in maintaining metabolic balance and ensuring proper oxygenation for both the fetus and the mother.

These changes are orchestrated by complex interactions between hormones, neurohumoral mechanisms, and structural adaptations.

During pregnancy, there are complex hemodynamic adaptations to support the fetus's development and meet the increased metabolic and functional needs of the maternal body.

One of the most notable adaptations is the increase in total blood volume, also known as pregnancy-related hypervolemia. Starting from the first trimester and continuing into the second, the plasma volume begins to increase rapidly, reaching about 40-50% above baseline values by the end of pregnancy.

Concurrently, the red blood cell mass also increases, but to a lesser extent, leading to a dilution of hemoglobin and hematocrit concentrations, a phenomenon known as pregnancy-related dilutional anemia.

This is not a pathological anemia but rather a physiological adaptation. Erythropoietin is a glycoprotein mainly produced in the kidneys, but also in the liver, and is responsible for stimulating bone marrow to produce red blood cells. In the context of pregnancy, there is an increase in erythropoietin levels, leading to the so-called pregnancy-related erythrocytosis.

This ensures adequate oxygen transport to the mother's tissues and supports the fetus's growth and development. Elevated erythropoietin levels are partly due to the relative hypoxia associated with increased plasma volume and other pregnancy-specific endocrine factors.

The increase in blood volume is essential for ensuring adequate cardiac output, which rises during pregnancy to meet increased demands. The enhanced blood volume also

supports placental perfusion, ensuring an adequate supply of nutrients and oxygen to the fetus. It also prepares the mother's body for blood loss during childbirth.

However, understanding these adaptations is essential for accurately interpreting laboratory values and distinguishing between normal adaptations and potential pathologies.

Cardiac output (DC) also increases during pregnancy by about 30-50% compared to pre-pregnancy values. Two primary parameters contribute to this increase: stroke volume and heart rate (FC).

Both parameters have elevated values during pregnancy. The increase in stroke volume is partly driven by plasma volume expansion and increased venous return secondary to hypervolemia.

The heart rate also rises, contributing to a 30-50% overall increase in cardiac output compared to pre-pregnancy levels. Hormones play an essential role in orchestrating these changes.

Relaxin is a peptide hormone produced by the ovaries and placenta, crucial in adapting the cardiovascular system to pregnancy. It induces vasodilation, contributing to decreased peripheral vascular resistance, thus favoring the rise in cardiac output.

Estrogen and progesterone, produced in large amounts by the placenta during pregnancy, also have multiple effects on the cardiovascular system.

Estrogen contributes to plasma volume expansion by increasing renin levels, and consequently, the renin-angiotensin-aldosterone system (SRAA), which regulates water and sodium balance.

This hormone also stimulates the production of nitric oxide (NO), a potent vasodilator. Progesterone, on the other hand, induces vasodilation, thus contributing to the decrease in peripheral vascular resistance and facilitating cardiac output increase.

Blood pressure (TA) is a vital hemodynamic variable carefully monitored during pregnancy, as its changes can have implications for both the mother and fetus. Typically, blood pressure progression during pregnancy follows a predictable pattern, with a drop in the first trimester followed by a gradual return to baseline or slightly above it in the third trimester. These blood pressure changes are influenced by hemodynamic and hormonal mechanisms. Vasodilation is evident during pregnancy.

Progesterone, with increased concentration during pregnancy, is one of the main factors inducing vasodilation. Its vasodilatory effect contributes to decreasing peripheral vascular resistance, leading to a drop in blood pressure, especially in the first trimester.

Along with progesterone, other vasoactive factors like nitric oxide play a crucial role in regulating vascular tone during pregnancy. Nitric oxide is a soluble gas with potent vasodilatory properties produced by the vascular endothelium.

The increased production and release of nitric oxide during pregnancy promote the relaxation of vascular smooth muscles, thus contributing to a decrease in blood pressure.

Heart rate and its changes during pregnancy are a crucial physiological adaptation designed to support the increased metabolic demand and optimal placental perfusion. Throughout pregnancy, the heart rate shows an upward trend. In the third trimester, it's common for the heart rate to be 10-15 beats/minute higher than before pregnancy.

This increased heart rate, coupled with a rise in stroke volume, contributes to the overall increase in cardiac output during pregnancy. Physiologically, the heart rate increase during pregnancy can be explained by several factors.

One of the main factors is the increased circulating level of hormones, especially estrogen and progesterone, which have a positive chronotropic effect. Also, the increased blood volume and oxygen demand, especially due to fetal and placental metabolism, stimulate baroreceptors and chemoreceptors, which in turn can modulate heart rate.

Peripheral vasodilation, observed during pregnancy, responds to increased blood volume and the fetus and placentas' heightened metabolic needs.

Vasoactive hormones like estrogen and progesterone play a role in this process, causing the relaxation of the smooth muscles of the vascular walls, thereby promoting vasodilation.

This vasodilation helps facilitate blood circulation, allowing optimal nutrient and oxygen transfer to maternal and feto-placental tissues.

Pregnancy also leads to a decrease in the renin-angiotensin-aldosterone. Studies have reported that the global prevalence of hypertension during pregnancy varies between 5% and 10% of all pregnancies, with higher incidents in developed countries.

Preeclampsia, characterized by hypertension and proteinuria, affects approximately 3-5% of pregnant women, while eclampsia, the severe stage of preeclampsia, occurs in about 0.05-0.1% of cases.

III. SPECIAL PART

It is structured from the results of 4 studies in which the effects of cardiovascular risk factors (RCV) and hypertensive disorders that appeared during pregnancy on the biological status of obstetric patients and the conception product were demonstrated.

In the first study, a cohort of 68 participants was recruited, of which 30 were pregnant women with RCV, and 38 did not present this risk. These participants were prospectively monitored during their pregnancies from 2020 to 2022 at the Department of Obstetrics and Gynecology of the "Pius Brînzeu" County Emergency Clinical Hospital in Timișoara, Romania. All women included in this study underwent cesarean section procedures at the same medical unit.

Data were collected regarding gestational weeks at the time of birth, birth weight, and APGAR scores evaluated by neonatologists for each participant. Statistical analyses were performed to compare neonatal effects between the two groups.

The results of this study highlighted significant differences between groups regarding APGAR scores ($p = 0.0055$), gestation weeks ($p = 0.0471$), and birth weight of newborns ($p = 0.0392$).

The conclusion underscores the importance of considering maternal cardiovascular health as a potential determinant of neonatal outcomes. Further research is needed to elucidate the underlying mechanisms and to develop strategies to optimize neonatal outcomes in high-risk pregnancies.

In another study, a total of 68 participants were included, of which 30 were pregnant women with cardiovascular risk factors (RCV), and 38 were women without RCV, who were monitored throughout their pregnancy.

All the women included gave birth by cesarean section at the same medical institution. Telomere length was measured in each participant using the quantitative polymerase chain reaction technique.

The results showed that telomere length was negatively correlated with RCV in pregnant women, with significantly shorter telomeres observed in the RCV group (average telomere length = 0.3537) compared to the non-risk group (average telomere length = 0.5728) ($p = 0.0458$).

The conclusions suggest that RCV during pregnancy may be associated with accelerated telomere shortening, which could have implications for the long-term health of both the mother and the child.

Further research is needed to investigate the potential mechanisms underlying this association and to identify interventions that could mitigate the negative effects of RCV on telomere length during pregnancy.

The third study included 86 pregnant women, dividing them into two groups: Group 1 (n=46, healthy pregnancies) and Group 2 (n=40, pregnancies with cardiovascular risk factors). Collected data included information on the mothers' demographic characteristics, smoking history, pre-existing conditions, and a range of laboratory measurements.

Neonatal outcomes were also recorded. The results showed that Group 2 had a significantly higher percentage of abnormal APGAR scores, congenital abnormalities, severe prematurity, and higher neonatal mortality rates, as well as differences in birth weight and therapy use. Regarding the laboratory measurements, Group 2 had significantly higher levels of total cholesterol (CT), low-density lipoprotein cholesterol (LDL-C), Apolipoprotein B (ApoB), Lipoprotein A (Lp(A)), triglycerides, and high-sensitivity C-reactive protein (hs-CRP).

The discussion highlighted the increased risk associated with pregnancies complicated by cardiovascular risk factors. Group 2 presented a more concerning clinical profile, with a higher prevalence of negative neonatal outcomes and different lipidic and inflammatory profiles, signifying a possible pathophysiological link.

The conclusion emphasizes different lipid profiles and adverse neonatal outcomes in pregnancies with cardiovascular risk factors, underscoring the urgent need for effective risk stratification and management strategies in this population.

In the last study, 83 participants were involved, of which 48.19% were diagnosed with hypertensive disorders of pregnancy (HDP). Levels of ApoB and Lp(a) were analyzed as potential cardiovascular biomarkers.

A comparative analysis was conducted to assess differences in ApoB and Lp(a) levels between normal pregnancies and those with HDP. The results showed that pregnant women diagnosed with HDP had significantly higher levels of ApoB (p-value = 0.0486) and Lp(a) (p-value < 0.0001) compared to those with normal pregnancies.

The association between elevated levels of ApoB and Lp(a) and HDP was evident even in the unique physiological context of pregnancy. The conclusions underline the importance of early identification and personalized management of cardiovascular risk factors in pregnant women, especially those at risk of HDP.

The findings highlight the potential of ApoB and Lp(a) as biomarkers for assessing cardiovascular risk during pregnancy. The multidisciplinary perspectives of the study

emphasize the need for comprehensive care and counseling, aiming to optimize cardiovascular outcomes in the postpartum period.

The research is based on mixed methodologies, including secondary data analysis and primary data collection through case studies and interviews. The main findings suggest that there's a significant correlation between maternal cardiovascular conditions and neonatal outcomes, with vital implications for obstetric and neonatal care.

IV. FINAL CONCLUSIONS

It has been demonstrated that pregnant women with cardiovascular risk factors (CRF) have an increased risk of neonatal complications.

These complications can have a lasting impact on the child's health and may require emergency medical interventions.

Among these complications are abnormal APGAR scores. Lower APGAR scores often indicate difficulties in the newborn's adaptation to life outside the womb and may require intensive medical care.

Additionally, maternal CRF is associated with severe prematurity, meaning that newborns are born before the standard term of 38 weeks of gestation. Severe prematurity can lead to a range of health complications for the newborn, including respiratory issues, insufficient organ development, and infections.

Another alarming aspect is the increased neonatal mortality among pregnant women with CRF.

This means there is a higher risk of the newborns not surviving the first days or weeks of life. This sad reality underscores the need for careful management of maternal CRF during pregnancy.