

CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST
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OBSTETRICS - GYNECOLOGY

PLACENTAL VASCULAR REMODELING IN
FETO-MATERNAL PATHOLOGY
SUMMARY OF THE DOCTORAL THESIS

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SUMMARY

Placental vascular remodeling is a crucial aspect of placental development and is essential for ensuring adequate perfusion of the fetus during pregnancy. In maternal-fetal pathology, this vascular remodeling can be altered, leading to significant clinical complications. Therefore, understanding the mechanisms underlying placental vascular remodeling in the context of maternal-fetal pathology is essential for developing strategies for early diagnosis, intervention, and prenatal management. This doctoral thesis aims to explore and deeply analyze these mechanisms, with the ultimate goal of contributing to the improvement of maternal-fetal healthcare and reducing the incidence of pregnancy-associated complications.

Research in the field of maternal-fetal pathology began to take shape more systematically starting in the 19th century, with advances in the understanding of the physiological processes of pregnancy and fetal development. Significant contributions from Franz Karl Naegele, who formulated the well-known "Naegele's rule" for calculating the probable date of delivery, and Eduard Heinrich Hensch, who described various pregnancy-related conditions, marked the initial steps in understanding and diagnosing maternal-fetal pathology. However, it is important to emphasize that research in this field has continued to develop and diversify over time, with technological advancements and the evolution of medical knowledge. Thus, while early contributions, such as those by Bumm in 1893, were fundamental to the development of maternal-fetal pathology, research in this field has continued to progress and expand in subsequent centuries.

The physiological changes that occur in the uterine vascular system during pregnancy are a crucial aspect of gestational physiology and have a significant influence on maternal-fetal health. Karl Bumm was a German physician who made significant contributions to understanding the physiological changes that occur in the uterine vascular system during pregnancy. In his 1893 work titled "Beitrag zur Kenntniss der Uterusgefäße während der Schwangerschaft" ("Contributions to the Knowledge of Uterine Vessels During Pregnancy"), Bumm documented his observations regarding the vascular changes that take place in the uterus throughout pregnancy. He described the increase in the number and diameter of uterine blood vessels, as well as changes in their histological structure, which are essential for ensuring adequate perfusion of the placenta and fetus. Bumm's work was an important

step in understanding the physiology of pregnancy and contributed to the foundation of medical knowledge in the field of maternal-fetal pathology.

In recent decades, research on placental vascular remodeling in maternal-fetal pathology has seen significant growth, benefiting from technological advances and a better understanding of the molecular and cellular mechanisms involved in this complex process. Numerous experimental models have been developed to investigate and elucidate the factors influencing placental vascular remodeling, including in vitro models, animal models, and advanced imaging techniques. These models have facilitated the study of interactions between various cells and environmental factors at the placental level and have allowed researchers to evaluate the impact of different interventions and treatments on the vascular remodeling process. However, despite the progress made, many aspects of this field remain unexplored and require further in-depth and detailed investigation. This doctoral thesis aims to contribute to this research effort by developing an innovative model from the perspective of integrated factors, both risk and imaging, and by investigating key aspects of placental vascular remodeling in maternal-fetal pathology.

The doctoral thesis proposes an innovative approach by integrating a complex model that takes into account the relevant risk factors for maternal-fetal pathology along with advanced imaging investigations. By combining these two fundamental elements, new perspectives are opened in understanding placental vascular remodeling and its impact on maternal-fetal health. The integration of risk factors into the proposed model allows for a more complete and accurate assessment of pregnancy-associated risk, while the use of advanced imaging investigations adds an additional dimension of detail and clarity in the analysis of vascular phenomena. This synergistic combination represents a significant step forward in maternal-fetal pathology research and promises to provide valuable tools for early diagnosis, prognosis, and management of this complex condition.

Placental vascular remodeling is the complex process by which the vascular network of the placenta forms and develops during pregnancy. The placenta plays a vital role in providing oxygen and nutrients to the fetus throughout embryonic and fetal development. Placental vascular remodeling is essential for ensuring efficient circulation between the placenta and the fetus, and dysfunctions in this process can have severe consequences on fetal development and maternal-fetal health. This process involves a series of changes in the placental blood vessels, including growth, branching, and vascular remodeling to ensure adequate perfusion and efficient exchange of substances between the mother and the fetus. Additionally, placental vascular remodeling is crucial for establishing and maintaining an

effective interface between maternal and fetal circulation, ensuring harmonious fetal development and preventing complications associated with placental insufficiency.

Preeclampsia is the most common and serious medical disorder that occurs during human pregnancy. This condition is found almost exclusively in humans, and childbirth remains the only effective treatment. Especially during the first pregnancy, pregnant women may experience high blood pressure, kidney dysfunction leading to proteinuria, and swelling in the hands, feet, and face. In severe cases, dizziness, headaches, and vision problems may occur. These symptoms are characteristic of preeclampsia. Without treatment, preeclampsia can progress to eclampsia, which is associated with seizures and other severe complications that threaten the lives of both the mother and the unborn fetus. Early diagnosis and effective management of this condition are crucial for preventing complications and ensuring a positive pregnancy outcome for both the mother and the fetus.

Preeclampsia is a condition that occurs exclusively during pregnancy, and currently, the only cure is the termination of the pregnancy, even if the fetus is not yet ready for birth. Preeclampsia and its associated complications account for a significant proportion of direct maternal mortality and perinatal mortality, contributing to 15% and 10% of these statistics, respectively. Preeclampsia is the indication for approximately 20% of labor inductions and 15% of cesarean sections. Additionally, this condition is responsible for 5-10% of spontaneous or iatrogenic preterm births.

Fetal growth restriction (FGR) is a complication diagnosed in approximately 10% of pregnancies and is associated with significant perinatal mortality and morbidity. It remains a pathology without antenatal treatment, where prenatal diagnosis and fetal monitoring are the only options to reduce stillbirth rates. If FGR is not diagnosed prenatally, the risk of intrauterine death is eight times higher. An estimated fetal weight below the 10th percentile is the definition for FGR. This single criterion is not specific as it does not differentiate between pathological fetal growth and a constitutionally small fetus. The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) includes in the definition of fetal growth restriction the abnormal pulsatility index of the uterine artery and umbilical artery (> 95 th percentile) along with estimated fetal weight or abdominal circumference below the 3rd percentile (Ghelnene, et al., 2024).

Both the diagnosis and proper management of intrauterine growth restriction (IUGR) cases remain a challenge for modern obstetrics. The variability in diagnostic criteria, monitoring methods, and the uncertain impact of various factors at each gestational age make this statement true; the obstetrician's challenge lies in accurate diagnosis with proper

gestational age assessment and, in accordance with these parameters, timing the birth for the best foreseeable neonatal outcome. Iatrogenic prematurity, superimposed on cases of intrauterine growth restriction due to uncertainty in fetal status assessment, significantly increases the mortality and morbidity associated with these cases.

The postnatal impact of IUGR should not be overlooked. Among preterm births, which are sometimes preferred to prevent intrauterine death, infants with IUGR have a difficult transition at birth when hypoxic stress is added due to uterine contractions. Common complications in babies with intrauterine growth restriction include poor thermoregulation, hypoglycemia, hypocalcemia, hyperbilirubinemia, polycythemia and hyperviscosity, feeding difficulties, and impaired immune function, necessitating close monitoring during the neonatal period and after discharge (Gheltene, et al., 2024).

The doctoral thesis was based on studies conducted by Gyokova et al. (2024), Figueras et al. (2021), and Maher et al. (2013), which correlate risk factors in placental disorders with Doppler imaging investigations. The study by Maher et al. (2013) highlights the utility of transvaginal ultrasound, which helps establish a significant correlation between identified risk factors for placental disorders and improves the effectiveness of screening and diagnostic methods (Ayati et al., 2017).

Moving forward, in this context, the doctoral thesis aims to evaluate risk factors from the perspective of existing literature, investigate the presence of these risk factors within the Romanian population, and determine how they interact with each other in the first stage. It is important to note that these factors and the outcome of their interactions vary from country to country. Thus, based on available data, and in line with the findings of research (Yingying et al., 2021; Saito, 2018) which reveal that these factors and their interactions differ significantly between countries, remarkable differences have been observed in the association with known risk factors between populations, triggering factors, risk factors, etiology, severity, and early diagnostic signs. The implications for preeclampsia may differ for the Romanian population compared to other regions of the world.

The ultimate goal of the second stage of the research is to correlate the clinical utility of uterine artery Doppler velocimetry as a predictor of adverse pregnancy outcomes. By integrating risk factors, imaging investigations, and their impact on pregnancy progression, this thesis aims to provide new insights and make significant contributions to the understanding and management of maternal-fetal pathology in the specific context of the Romanian population. Ultimately, all these factors will form a model that offers predictions regarding the future of the pregnancy and its outcomes.

From a methodological perspective, the research involved two stages: a stage of knowledge review and a descriptive quantitative study.

For the first stage of the research, secondary information sources were studied—specifically, specialized literature. This stage is represented by a knowledge review through which the factors that can impact placental vascular remodeling, manifested through the two clinical entities—preeclampsia and intrauterine growth restriction—were identified. Furthermore, scientific articles and guidelines from major representative bodies and professional associations worldwide were studied.

In the second stage, through quantitative research, demographic, medical, and imaging data were collected using a mixed tool—a questionnaire-observation sheet—completed during routine consultations, on the occasion of first and second trimester morphological ultrasounds, and based on the completion of data following imaging investigations, specifically Doppler ultrasound of the uterine arteries.

The aim of this doctoral thesis is to identify the risk factors influencing changes in placental vascular circulation and to correlate them with Doppler ultrasound of the uterine arteries in the first and second trimesters. The goal is to integrate these findings into a model that can be clinically applied to predict adverse pregnancy outcomes in low-risk women.

The proposed model aims to assess the risk of complications during pregnancy, based on two main components: risk factors and imaging factors obtained through ultrasonography, specifically the pulsatility index (PI) and the resistance index (RI).

Improving the prognosis of pregnancies complicated by the effects of deficient vascular remodeling depends on optimizing the development of screening tests and the ability of clinicians to early detect pregnant women at risk of developing complications specific to placental vascular remodeling. This phenomenon occurs early in pregnancy and its impact becomes apparent only when intervention methods are extremely limited. Currently, according to the ASPRE study, there are validated screening models for preeclampsia and early intrauterine growth restriction.

Thus, based on the available data and the fact that research such as (Yingying, et al., 2021) and (Saito, 2018) reveals that these factors and the results of their interactions differ from country to country, remarkable differences have been observed in the association with known risk factors between populations, the triggering factors, risk factors, etiology, severity, and early diagnostic signs. The consequences of preeclampsia may differ for the population of Romania compared to other regions of the world.

Considering that in Romania, the analysis of PLGF, which can refine the risk calculation for preeclampsia, is not reimbursed and is not accessible to the majority of the population, it is deemed necessary to validate and compare combined screening methods. This includes the possibility of evaluating high-risk pregnancies through easily accessible and reproducible means in centers where first-trimester screening and second-trimester morphological ultrasound are performed.

Current screening methods for preeclampsia rely on identifying maternal risk factors, biochemical markers, and Doppler imaging evaluations. However, there is no consensus for identifying the risk of intrauterine growth restriction (IUGR), as it is often implicitly assumed that IUGR will develop within the context of the preeclampsia syndrome (Poon, et al., 2019).

Regarding the methodology, a total of 203 pregnant women with singleton pregnancies were included in this prospective observational study and were evaluated for basic demographic and obstetric data.

These women underwent ultrasound evaluations during the first and second trimesters, including Doppler assessment of the uterine arteries bilaterally to determine pulsatility index (PI) and resistance index (RI) values, as well as the presence of a protodiastolic notch.

From a methodological perspective, the research consisted of two stages:

- I. The qualitative research stage, involving a review of the specialized literature
- II. Quantitative research based on the observation sheet instrument

1. Research from the Specialized Literature

For the first stage of the research, secondary information sources were studied. This stage involved a literature review, consisting of an analysis of the current state of knowledge, which helped identify factors that can impact placental vascular remodeling, manifested through two clinical entities: preeclampsia and intrauterine growth restriction (IUGR). Scientific articles and guidelines from major representative bodies and professional associations worldwide were studied.

This research had a predominantly exploratory role, aiming to determine all factors influencing the occurrence of intrauterine growth restriction from multiple perspectives. Only organizations offering relevant and detailed studies and information on the studied topic were selected, including ISUOG, ESGO, ACOG, FMF, AAP, and WHO. Information sources retained in the work were considered reliable and valid, with validity and reliability determined by the recognition of the institutions/authors.

The studies considered are as follows: ASPRE: Analyzing target values for Doppler velocimetry, TRUFFLE: Staging of IUGR, ISUOG: Reference model and quality criteria for Doppler measurements, FMF: Establishing percentiles, Perinatology: Calculator section, Articles published in scientific journals and specialized literature

2. Quantitative Research

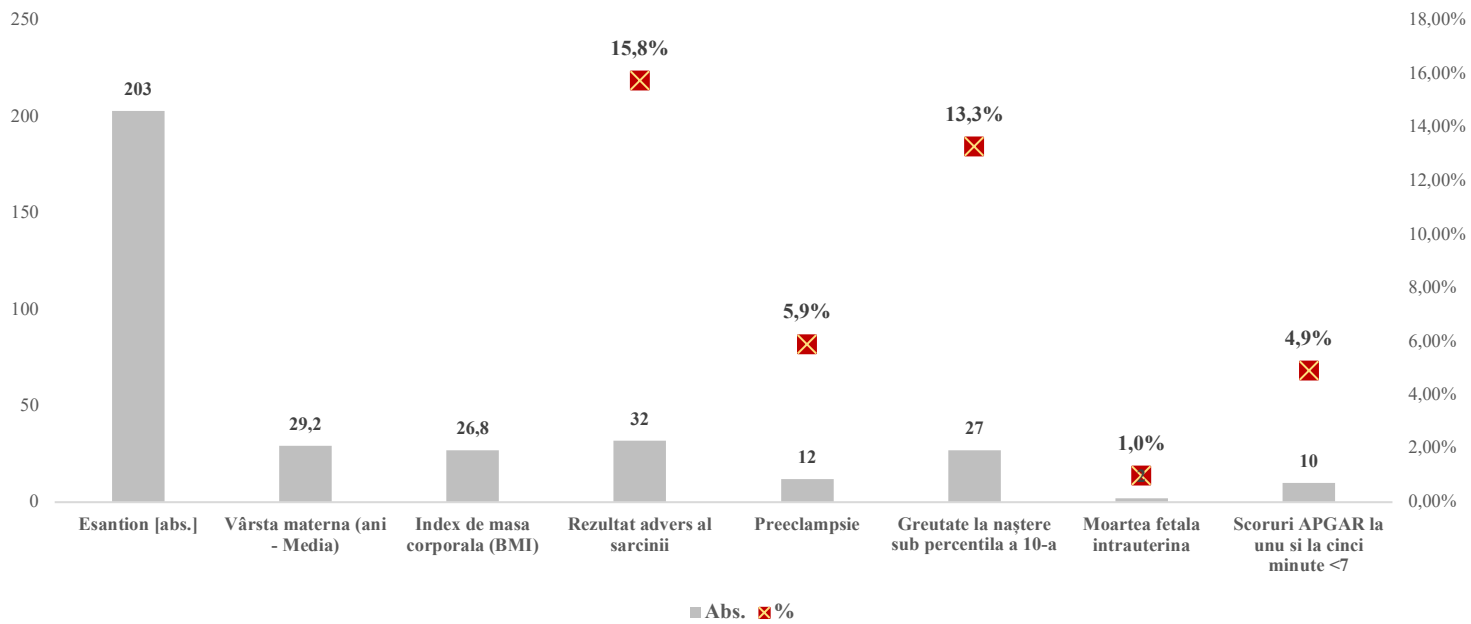
In the second stage, quantitative research was conducted to collect demographic, medical, and imaging data using a structured questionnaire – an observation sheet. This was filled out during routine consultations, specifically during first and second trimester morphology ultrasounds, and supplemented with data from imaging investigations, particularly Doppler ultrasound of the uterine arteries.

Research Objectives

1. Determining the factors that influence the prognosis of fetal growth restriction;
2. Evaluating the importance of the factors that influence the prognosis of fetal growth restriction;
3. Determining the specific methods, techniques, and tools that can be used in the management and improvement of the prognosis in fetal growth restriction;
4. Determining early detection and management strategies that can be successfully applied to improve the prognosis;
5. Integrating information and determining the scheme and conceptual model for the diagnostic strategy;
6. Representativeness of the Resistance Index (RI) and the Pulsatility Index (PI) in establishing the risk of adverse pregnancy outcomes.

The mean PI and RI in the analyzed population were 1.7 and 0.81, respectively, from the first trimester and the second trimester. The uterine artery PI and RI values for evaluations from the first and second trimesters were significantly higher in patients who developed pregnancy complications compared to normal women. The mean PI > 95th percentile for gestational age at 11-13 weeks of gestation and at 20-24 weeks of gestation were present in 43 (21%) and 19 (9.5%) of the patients, respectively. The 90th and 95th percentiles of the uterine artery RI were calculated to be 2.6 and 2.2, and 0.76 and 0.80, respectively, for the first trimester.

Demographic Characteristics and Outcome Data of the Study Population



In this research, a mathematical and graphical model was developed to evaluate the risk of pregnancy complications associated with specific risk factors. The proposed model uses two main functions (“f” and “F”) to quantify the risk:

- The first function, $f(x,y,z,w,u,v)=ax+by+cz+dw+eu+fv$, integrates the values of the risk factors, while the second function,
- $F=PI \times RI$

combines the pulsatility index (PI) with the resistance index (RI). Within each category of risk factors, an average value was established, above which the risk is considered high. The coefficients (a, b, c, d, e, f) are calibrated based on these average values, having a value of 1 for risk factors below the established average and a value determined by the formula for those exceeding the average. Thus, the model provides a robust and accurate method for risk assessment, allowing personalized and preventive interventions in patient management.

Within each category, for each risk factor, there is an average value, above which the risk is increased. Thus, the value of the coefficient (a, b, c, d, e, f) for values below the average is 1 (1x), meaning these coefficients do not impact the function score. If the coefficient value is above the average, its value is the one resulting from the research

conducted. Specifically, if the patient exceeds the average in a risk factor, the coefficient taken will be the one that indicates a higher risk of complications.

The model is graphically represented in an XoY coordinate system, with the origin at point (0,0), where the X and Y coordinates represent the values of the variables obtained from the research. The X-axis (OX) and the Y-axis (OY) will be configured to reflect the full range of possible values for the respective scales.

Detailing the Coordinate System

1. Origin of the Coordinate System

The origin of the graph is set at point (0,0), meaning that both the OX and OY axes start from the value of 1. This choice of origin is used to avoid zero values and to ensure better visualization of the data, especially in cases where values can be very small. The maximum values of the X and Y axes will be determined based on the highest values observed in the research for “f” and “F”, so the graph covers the entire range of possible results.

2. OX Axis

On the OX axis, the results of applying the model for each individual will be noted in relation to the risk factors and the function “f”. The results will be calculated using the formula. The values on the OX axis will vary depending on the maximum possible values obtained from the research. Thus, on the OX axis, the results of applying the model for each individual will be noted, corresponding to the risk factors and the function “f” as defined above.

3. OY Axis

On the vertical axis (OY) of the graph, the results of the function “F” will be represented, which combines the two important variables in the evaluation of imaging investigations: PI (Pulsatility Index) and IR (Resistance Index).

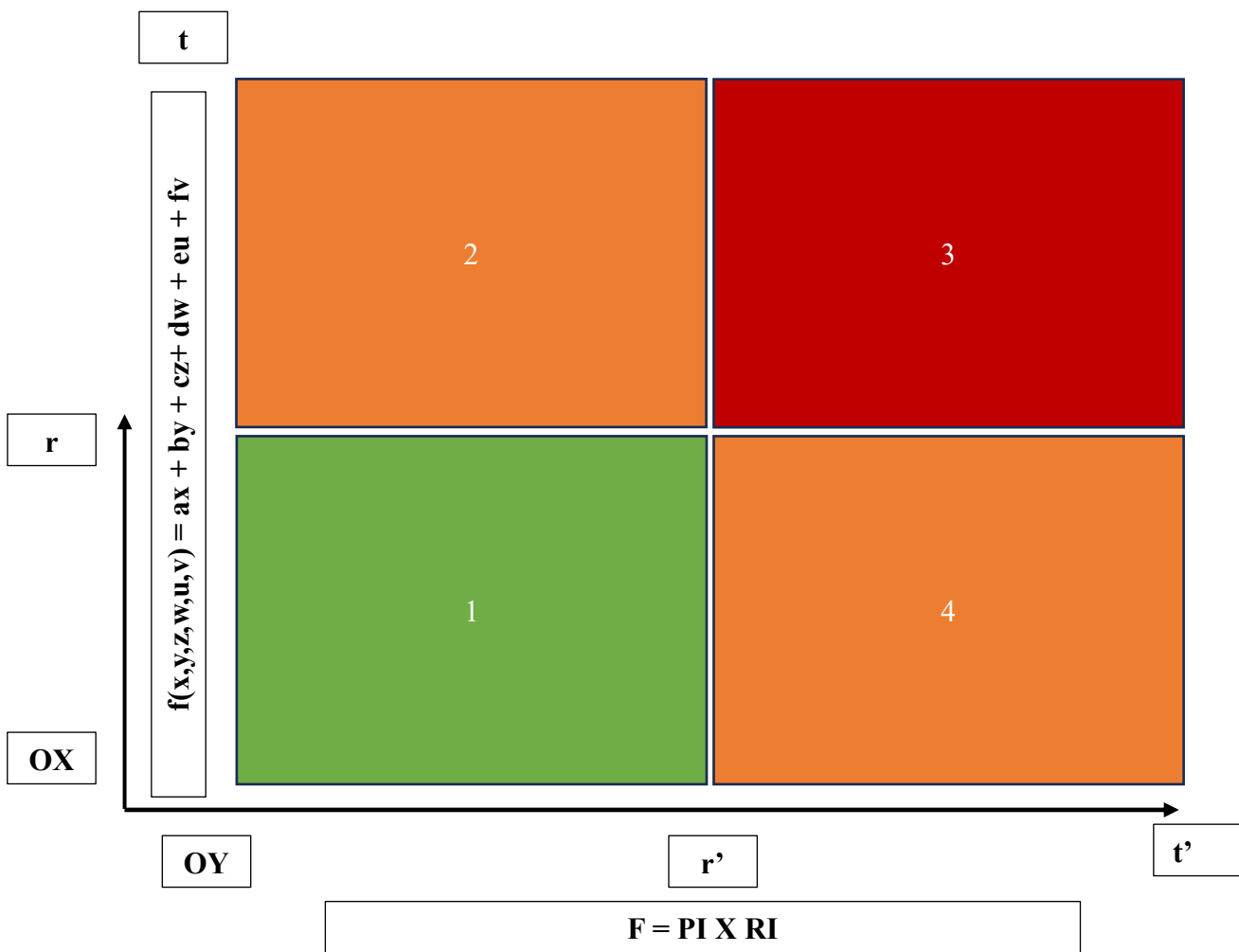
Since the OY axis can represent only one value at a time, the function “F” is defined as the product of PI and IR, i.e., $(F = PI \times IR)$. The choice of this product as a graphical representation has significant meaning. Essentially, multiplying these two factors allows for the simultaneous capture of each one's influence on the final outcome, reflecting how abnormal values of one factor can impact the prognosis.

By using the product of PI and IR, it is highlighted that each factor, when exhibiting abnormal values, negatively influences the overall outcome. Moreover, if both factors present abnormal values, the combined effect is amplified, having a more significant impact on the prognosis and interpretation of imaging investigations. This approach allows for an

integrated and detailed assessment, ensuring that both individual and combined influences of abnormal values are adequately considered for precise diagnosis and effective risk management.

Thus, graphs utilizing the function $(F = PI \times IR)$ provide a clear and efficient visualization of how abnormal values of both variables contribute to prognostic determination, aiding in the identification and interpretation of the clinical significance of imaging results.

Proposed Model (graphic)



Quadrants and Risk Interpretation:

Quadrant I (bottom left): LOW RISK

- Position: Values on both axes are low.
- Interpretation: Both the function $f(x,y,z,w,u,v)$ and the function F are low. This quadrant suggests low risks, indicating that the values of risk factors are low and that the product of

PI and RI does not significantly contribute to risk. It is a positive sign for evaluating low risks of complications.

Quadrant II (top left): MODERATE-HIGH RISK (factors)

- Position: Values on the X-axis are high, while values on the Y-axis are low.
- Interpretation: In this case, the values of the function $f(x,y,z,w,u,v)$ are high, but the function F is low. This suggests that individual risk factors are elevated, but the product $PI \times RI$ is not large enough to significantly amplify the risk. The risk may be heightened due to individual factors, but the combined effect is not sufficient to indicate a high overall risk.

Quadrant III (top right): HIGH RISK

- Position: Values on both the X-axis and Y-axis are high.
- Interpretation: In this quadrant, both the values of the function $f(x,y,z,w,u,v)$, which integrates all risk factors, and the function F , which reflects the product of PI and RI, are high. The risk in this quadrant is considered very high, indicating a significant impact of both functions on the total risk of complications. This suggests the presence of elevated values for all risk factors and a high combined predisposition, reflecting an amplified risk.

Quadrant IV (bottom left): HIGH RISK (Imaging)

- Position: Values on the X-axis are low, and values on the Y-axis are high.
- Interpretation: In this quadrant, the function F is high, while the values of the function $f(x,y,z,w,u,v)$ are low. This may indicate that although the individual risk factors are relatively low, their combination ($PI \times RI$) has a significant impact on the risk. This suggests that the combined effect is more important than the individual value of the factors.

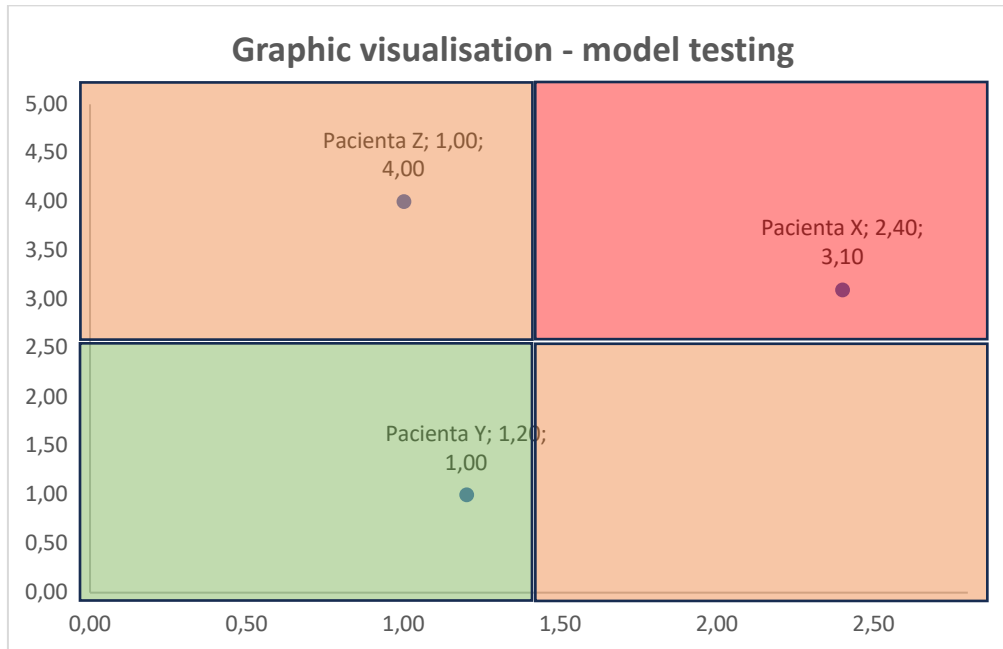
To validate and verify the developed model, tests were conducted on a sample of three pregnant women, referred to as X, Y, and Z. The purpose of these tests was to evaluate the efficiency and accuracy of the proposed mathematical and graphical model, which integrates specific risk factors and the functions $f(x,y,z,w,u,v)$ and $F = PI \times RI$ - pulsatility index (PI) and resistance index (RI).

Validation of Model Functionality

The tests conducted on the three pregnant women demonstrated that the algorithm operates as expected, accurately indicating the risk level associated with each patient. The results confirmed that the model can be used to evaluate the risks of complications in pregnancy, effectively integrating specific risk factors and their combination.

Efficiency and Precision. The model has shown that it can provide accurate risk estimates, correctly reflecting the risk level based on the input values. This suggests that the model is well-calibrated and can be used for clinical evaluations in the context of pregnancy risks.

Graphical Visualization of Model Testing



Placental vascular remodeling is a crucial aspect of placental development, having a direct impact on fetal perfusion during pregnancy. In cases of maternal-fetal pathology, this process can undergo changes that contribute to significant complications. Therefore, a detailed understanding of the mechanisms involved in placental vascular remodeling in the context of maternal-fetal pathology is essential for the development of advanced strategies for early diagnosis, intervention, and prenatal management. This doctoral thesis has thoroughly investigated and analyzed these mechanisms, contributing to improved maternal-fetal medical care and the reduction of pregnancy-related complications in clinical practice.

Nevertheless, there are still many unexplored aspects and challenges that require deeper and more detailed investigation in future research. This doctoral thesis aims to contribute to this ongoing research effort by developing an innovative model that integrates risk factor perspectives and advanced imaging technologies. A detailed investigation of the key aspects of placental vascular remodeling in the context of maternal-fetal pathology represents an essential direction for improving medical management and reducing the negative impact of pregnancy-related complications.

In conclusion, moving forward, this doctoral thesis succeeded in evaluating risk factors from the perspective of existing literature and investigating their presence among the Romanian population by analyzing their interactions. The ultimate goal of the research was to assess the clinical utility of uterine artery color Doppler ultrasound as a predictor of adverse pregnancy outcomes. By integrating risk factors, imaging investigations, and their impact on pregnancy progression, this thesis brings new perspectives and significant contributions to the management of maternal-fetal pathology in the specific context of the Romanian population. The proposed model allows for more accurate prediction of pregnancy progression and outcomes, with the potential to improve prenatal management and reduce the risks associated with placental complications.

The proposed model aims to assess the risk of complications during pregnancy, based on two main components: risk factors and imaging factors obtained through ultrasonography, specifically the parameters PI (prenatal indicator) and RI (imaging indicator).

In the context of future developments, the proposed model can be improved by including other relevant pregnancy risk factors, such as the patient's medical history and other family antecedents. Additionally, advanced statistical analysis and machine learning can be utilized to optimize the model and identify complex interactions between different risk factors. Continuous validation of the model based on current clinical and research data is essential to ensure its accuracy and relevance in various medical contexts. Integrating longitudinal data, i.e., collecting information throughout the entire pregnancy and postpartum period, can provide a more comprehensive risk assessment and more precise adaptation of prenatal management. Furthermore, advances in imaging technology may allow for the development of more precise methods for evaluating the fetus's condition and for completing and enhancing the existing model. Implementing this model in clinical practice could support physicians in assessing and managing pregnancy-related risks, providing personalized guidelines for each patient.

In the future, artificial intelligence (AI) can also be used to analyze and interpret complex medical data, including patients' medical histories and genetic data, to identify new risk factors and improve the accuracy of predictions. By utilizing machine learning algorithms, AI can uncover patterns and correlations between different risk factors, thus providing a deeper understanding of pathological mechanisms and pregnancy-associated risks. AI can also be involved in the development of more precise and faster screening and diagnostic imaging tools, which can detect abnormalities and pregnancy complications early on. By integrating longitudinal data and continuously updating the model, AI can offer more

rigorous monitoring of pregnancy progression and adapt risk management strategies in real-time. Ultimately, AI can facilitate communication and collaboration between doctors, researchers, and patients, contributing to the overall improvement of maternal-fetal healthcare.

List of Published Scientific Papers

1. Elena-Adriana Ghelmene, Nastasia Serban, Manuela Cristina Russu, *Sonographic Placental Aspects in Fetal Growth Restriction*, Modern Medicine, 2024, Vol. 31, No. 1, <https://medicinamoderna.ro/wp-content/uploads/2024/03/Sonographic-Placental-Aspects-in-Fetal-Growth-Restriction.pdf>, <https://doi.org/10.31689/rmm.2024.31.1.7>
2. Elena-Adriana Ghelmene, Nastasia Serban, Manuela Cristina Russu, *Fetal Growth Restriction in Patients with Adenomyosis. Incidence and Mechanism*, Modern Medicine, 2024, Vol. 31, No. 2, <file:///Users/i/Documents/Teza%20de%20doctorat%20Adriana%20Ghelnene/Fetal-Growth-Restriction-in-Patients-with-Adenomyosis.-Incidence-and-Mechanism.pdf>, <https://doi.org/10.31689/rmm.2024.31.2.113>
3. Manuela Russu, Adriana Ghelmene, Daniela Degeratu, Șerban Nastasia - Diagnosis and treatment difficulties in a recurrent non- gestational primary breast abscess due to Mycobacterium tuberculosis infection. Case Report. Literature Review.
4. Ilinca Gussi, Adina Diaconescu, Adriana Ghelmene, Amalia Stanescu, *Metabolic disruption unchanged by current parental care strategies in neonates from preexisting diabetic mothers: Data from a 3rd level reference center in Bucharest Romania*, European Journal of Obstetrics and Gynecology and Reproductive Biology 234 (2019): e60.
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