

UNIVERSITY OF MEDICINE AND PHARMACY

"CAROL DAVILA", BUCHAREST

DOCTORAL SCHOOL

***THE ROLE OF FETAL NOMOGRAMS ULTRASOUND
DETERMINED IN THE ROMANIAN POPULATION***

SUMMARY

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Introduction

Advances in ultrasound have facilitated the evaluation of organ measurements that are not part of the known standard, but which can be very useful in perinatal pathology.

In recent years, the size of the fetal thymus has been investigated, not only as a marker of genetic defects but also as a predictive factor in intrauterine growth restriction, preterm birth, preeclampsia, chorioamnionitis and neonatal sepsis[1–3]. Fetal adrenal ultrasonography is also increasingly being performed, with studies showing that its biometry can be used to predict pregnancy complications such as preterm birth, gestational diabetes, and intrauterine growth restriction[4].

The coverage of thymus nomograms in the fetal population can be the basis for the identification of fetuses at risk of thymic hypoplasia or hyperplasia, which is essential from the point of view of detecting potential congenital immunological disorders[5].

Adrenal glands are vital for human survival, primarily due to steroidogenesis, playing a vital role in prenatal regulation of intrauterine homeostasis, fetal development and maturation, and initiation of parturition[6]. Congenital adrenal hyperplasia is one of the pathological conditions that cause adrenomegaly in fetal life, which, if diagnosed and treated early, can have a favorable outcome and prevent morbidity and mortality. Bilaterally enlarged fetal adrenal glands during the prenatal period may be the only marker for congenital adrenal hyperplasia[7].

The limited number of publications may be due to differences in definitions, measurement of organ size or volume, and ultrasound methods, and more studies are needed to add evidence on this topic in order to guide clinical care and improve perinatal outcomes.

Therefore, there was a need to define and provide nomograms that could be used in daily practice, providing a useful reference point.

Thus, considering the importance of developing screening tools in obstetrics in the Romanian population, the present study aimed to determine the biometry of the fetal thymus and fetal adrenal gland and develop nomograms that could be used as a prognostic indicator of perinatal morbidity . We also evaluated the association between the reduced size of the fetal thymus measured by ultrasound and intrauterine growth restriction, and by means of fetal adrenal biometry we evaluated the prediction of preterm birth in pregnant women with

symptoms of preterm birth. This research is the first of its kind for the Romanian population, as there are no studies carried out in Romania until now that evaluate the ultrasound parameters of the fetal thymus and adrenal glands.

Approximately 30 million newborns are affected by intrauterine growth restriction per year in developing countries[8]. To prevent the complications associated with intrauterine growth restriction, it is important to detect the condition early and institute appropriate surveillance to reduce associated morbidity and mortality.

Preterm birth remains a major cause of perinatal morbidity and mortality worldwide. Compared to full-term births, preterm birth carries a 7-fold higher risk of neonatal death. Therefore, the identification of women at risk of premature birth is one of the essential prerequisites for effective intervention and improvement of perinatal outcomes[4].

The use of thymic nomograms could provide the possibility of detecting intrauterine growth restriction and primary immunodeficiencies, which are accompanied by abnormalities in the size of this organ or even its absence. Moreover, ultrasound of the fetal thymus can be a screening test for 22q11.2 depletion or Di George syndrome[9].

In addition to the prediction of premature birth, the role of the adrenal gland in fetal metabolism and fetal organ maturation are the main reasons to pay more attention to this vital organ, which is still a great enigma.

Nomograms developed based on multiple factor logistic regression analysis provide accurate predictions in various situations. It represents a graphical presentation of a prediction model that is widely used to predict the prognosis of diseases, and in recent years, obstetricians and gynecologists have begun to use them more widely[10,11].

GENERAL PART

Chapter 1. Intrauterine growth restriction

1.1 Definition and classification

Intrauterine growth restriction (IUGR) is one of the most common complications of pregnancy, which can have serious consequences for both the mother and the fetus or newborn. Fetuses with growth restriction are at increased risk of fetal death in utero, neonatal death, premature birth, neonatal morbidities and neurodevelopmental disorders. Long-term risks include chronic disorders such as obesity, diabetes, metabolic syndrome, and cardiovascular disease[12].

There are two types of intrauterine growth restriction: asymmetric and symmetric. Type I or asymmetric represents 70-80% of IUGR cases. It appears later, in the third trimester of pregnancy, and is characterized by the "brain sparing" phenomenon. The most common etiology is uteroplacental insufficiency. Ultrasound parameters show reduction in abdominal circumference, with biparietal diameter, cranial circumference and femur length within normal limits[15,16]. Type II or symmetrical represents about 20-30% of IUGR cases. It occurs early in pregnancy and is usually caused by a genetic disorder or intrinsic infection of the fetus. Antenatal sonographic evaluation of these fetuses shows a proportional decrease in biparietal diameter, cranial circumference, abdominal circumference, and femoral length. In terms of mortality and morbidity, the prognosis for fetuses born with symmetric IUGR is worse than for fetuses with asymmetric IUGR[17].

IUGR can be classified according to onset, if it occurs early or late in pregnancy. There is consensus that the cutoff should be the gestational age at diagnosis before or after 32 weeks [18]. This classification differentiates two phenotypes determined by the severity of placental damage and the adaptive mechanism in response to hypoxia[19]

Early-onset intrauterine growth restriction

Early-onset IUGR is less common and accounts for 20-30% of all cases. Association with preeclampsia is common [20], and placental histology of preterm neonates with IUGR shows uteroplacental insufficiency and abnormal blood supply [21].

In early-onset IUGR, the rate of perinatal morbidity and mortality is high. According to the results reported by the TRUFFLE trial, perinatal death occurred in 8% and 31% of infants meeting the criteria for a death or severe morbidity outcome, with sepsis (18%) and bronchopulmonary dysplasia (10%) being the major contributors. Less common complications were germinal matrix hemorrhage (2%) and cystic periventricular leukomalacia (1%).

Late-onset intrauterine growth restriction

IUGR with late onset represents 70-80% of all cases and the association with preeclampsia is lower [20]. Histologically, it is characterized by the presence of uteroplacental vascular lesions, especially infarcts, and the incidence of these lesions is lower than in early fetal growth restriction [23]. The degree of placental damage is moderate, thus, the Doppler velocimetry of the umbilical artery is within normal limits in most cases. In contrast, there is an increased association of abnormal cerebroplacental ratio values and middle cerebral artery (MCA) PI. Advanced signs of fetal damage with changes in ductus venosus flow are rare [24]. Because the fetus is more mature, there is a reduced tolerance to hypoxia and a greater risk of acute fetal damage and intrapartum fetal distress. Therefore, late IUGR may lead to rapid deterioration or death without a predictable pattern of deterioration, as in early IUGR [25].

1.2 Epidemiological data of intrauterine growth restriction

Intrauterine growth restriction affects approximately 3%-7% of pregnancies[29]. The incidence of IUGR is six times higher in underdeveloped countries compared to developed countries, and this incidence may be even higher in low- and middle-income countries because many children are born at home without birth registration. The incidence of IUGR differs by country and race and increases with decreasing gestational age[30]. Women with preeclampsia who have a history of intrauterine growth restriction have a 20% recurrence rate in future pregnancies. Approximately 40% of cases are idiopathic, and out of 60% of cases with identifiable causes, 1/3 are represented by genetic anomalies, and the rest are due to environmental factors[31].

1.3 Etiology of intrauterine growth restriction

Causes of intrauterine growth restriction are generally described as falling into three categories: maternal, fetal and placental.

Fetal causes

IUGR in the first half of pregnancy is mainly caused by intrinsic factors such as chromosomal aberrations or infections, while IUGR in the second half of pregnancy is mainly caused by extrinsic factors leading to placental insufficiency. Trisomies are often associated with fetal growth restriction, which is more severe with trisomy 18 compared to trisomies 13 and 21.[26]

Maternal causes

Birth weight depends on many factors, including race, sex, parity, maternal weight, and height.[27,28] Fetal nutrition is dependent on the mother's ability to supply oxygenated blood. Maternal causes of IUGR are generally related to placental insufficiency which is the main reason, accounting for up to 3% of all pregnancies. The pathogenesis is not fully elucidated, but it appears that defects in placental circulation affect the transport of nutrients to the fetus and therefore lead to IUGR.

Placental causes

Placental causes in IUGR are abruptio placentae, placental infarction, placental mosaicism, velamentous insertion of the umbilical cord, as well as placenta accreta. Genetic and environmental factors may influence early placental development, inappropriate trophoblast invasion, and the immunoregulatory environment. These processes, in turn, can trigger altered nutrient transfer, the hypoxic response, and a variety of inflammatory responses that are linked to adverse perinatal outcomes[29].

1.4 Doppler velocimetry in intrauterine growth restriction

Doppler velocimetry plays an important role in identifying, tracking and establishing the conduct of pregnancies with IUGR. Utero-placental insufficiency can be quantified by evaluating the uterine and umbilical arteries, and changes in cardiovascular adaptation can be evaluated by Doppler velocimetry at the level of the ACM and the ductus venosus

1.5 Ultrasound evaluation of the fetal thymus – literature review

The relationship between nutrition and immunity is widely recognized in the literature[30]. Chronic malnutrition can be identified in pregnancies with placental insufficiency and growth restriction during intrauterine life. There is post-mortem research in infants demonstrating that reduced thymus weight is associated with IUGR, an effect attributed to lymphoid tissue atrophy[31].

Chapter 2. The role of the fetal adrenal gland in preterm birth – literature review

Preterm birth is a major complication and remains the leading cause of neonatal morbidity and mortality worldwide. An estimated 15 million babies are born prematurely every year worldwide. In 184 countries, preterm birth rates ranged from 5 to 18%[32]. In Europe and other developed countries, reported rates are between 5-9%[33].

Fetal adrenal gland size is used as a quantitative measure of fetal adrenal gland activity and studies show that it may be predictive of spontaneous preterm birth[34].

PERSONAL CONTRIBUTIONS

Chapter 3. Working hypothesis and general objectives

The present work is structured in 4 studies:

- The first study aims to establish the reference intervals of the size of the fetal thymus between 24 and 41 weeks of gestation, more precisely for the maximum transverse diameter. Thymus morphometry is generally used to monitor the immunological status of fetuses and newborns. Many studies have shown that fetal thymus size is used as a prognostic indicator for certain disorders in pregnancy, such as preterm labor, preeclampsia, intrauterine growth restriction, and gestational diabetes.
- The second study aims to establish reference intervals of the size of the fetal adrenal glands for gestational ages between 24 and 41 weeks of gestation.
- The third study aims to evaluate the prognostic value of fetal thymus size in intrauterine growth restriction.
- The fourth study aims to evaluate the prediction of preterm birth within 7 days in pregnant women with symptoms of spontaneous preterm birth using fetal adrenal gland size and comparing this prediction with cervical length measurement.

Chapter 4. Fetal thymus nomograms for clinical practice

4.1 Introduction: Working hypotheses and general objectives

Establishing the reference intervals of the normal size of the fetal thymus between 24 and 41 weeks of gestation with the help of ultrasound, in the Romanian population, considering the important contribution brought to the postnatal fetal outcome

4.2 Material and method

The research in this thesis is framed as a prospective study. The total statistical batch of patients included in study I was composed of 120 patients, who presented themselves between October 2018 and December 2023 at the Bucur Maternity Hospital and at the "Sfântul Pantelimon" Emergency Clinical Hospital, Bucharest.

4.3 Results

In our study, based on statistical analysis, we found that the thymus grew in a relatively linear manner with increasing gestational age and the standard deviations of thymic dimensions had wider distributions with advanced gestational ages.

4.4 Discussions

The introduction of fetal thymus nomograms into routine ultrasound examinations could help in monitoring disorders related to intrauterine infections, intrauterine growth restriction or preterm labor.

Chapter 5. Nomograms of the fetal adrenal gland for clinical practice

5.1 Introduction: Working hypotheses and general objectives

The objective of this study was to construct nomograms of fetal adrenal glands measured by ultrasound, between 24-41 weeks of gestation, in the Romanian population, as well as to identify the relationship between gestational age and adrenal gland size.

5.2 Material and method

The research in this thesis is framed as a prospective study. The total statistical batch of patients included in study I was composed of 120 patients, who presented themselves between October 2018 and December 2023 at the Bucur Maternity Hospital and at the "Sfântul Pantelimon" Emergency Clinical Hospital, Bucharest.

5.3 Results

We used linear regression analysis, creating a model with a dependent variable (adrenal gland) and an independent variable (gestational age). Data were analyzed in terms of mean \pm standard deviation for the 5th, 10th, 50th, and 90th percentiles of whole fetal adrenal gland and fetal area for each gestational week in our cohort.

5.4 Discussions

Several studies have evaluated intrauterine adrenal gland size in correlation with gestational age, and the results suggest that fetal adrenal gland enlargement can be used to predict complications during pregnancy such as preterm birth, gestational diabetes mellitus, and intrauterine growth restriction[4,194]

Chapter 6. Prognostic value of fetal thymus size in intrauterine growth restriction

6.1 Introduction: Working hypothesis and objectives

The aim of this study was to assess the size of the fetal thymus in fetuses with intrauterine growth restriction by ultrasonographic measurement of the maximum transverse diameter and to compare it with the size of the thymus of healthy fetuses.

6.2 Material and method

The research in this thesis is framed as a prospective study. The total statistical group of patients included in study III was composed of a group of 131 pregnant women with a gestational age between 24 and 41 weeks, with intrauterine growth restriction and a control group of 120 pregnant women with an uncomplicated pregnancy, who presented themselves between October 2018 and December 2023 at the Bucur Maternity Hospital and at the "Sfântul Pantelimon" Emergency Clinical Hospital, Bucharest.

6.3 Results

The results of the study reveal that the transverse diameter of the thymus presents much lower values in the case of patients with intrauterine growth restriction. We also found a strongly statistically significant correlation between thymus diameter and gestational age, DBP, AC, FL and estimated fetal weight.

6.4 Discussions

Other studies also showed that the anteroposterior and transverse diameters of the fetal thymus increased with gestational age, and in IUGR, these parameters were lower than those of the thymus of healthy fetuses of the same gestational age[212].

Chapter 7. Establishing the role of fetal adrenal gland size determined by ultrasound in the prediction of premature birth in the Romanian population

7.1 Introduction: Working hypotheses and objectives

Evaluation of the prediction of preterm birth within 7 days in pregnant women with symptoms of spontaneous preterm birth using whole fetal adrenal gland size and comparison of this prediction with cervical length measurement.

The classification of the research group into a risk group according to the evaluation of maternal sociodemographic characteristics, which will guide us on the definition of that population suitable for the use of adrenal gland biometry as a marker of premature birth.

7.2 Material and method

This research is framed as a prospective study. The total statistical group of patients included in study IV was composed of 105 pregnant women with symptoms of premature labor, with a gestational age between 24 and 36 weeks, and a control group of 120 pregnant women with an uncomplicated pregnancy, with a gestational age between 24 and 41 weeks.

7.3 Results

The statistical analysis shows that the 5 analyzed parameters can be ranked as follows (in descending order) from the point of view of performance in predicting the risk of preterm birth ≤ 7 days: Width of fetal area right adrenal gland, Length of fetal area right adrenal gland, Total width right adrenal gland, Total length right adrenal gland, Cervical length.

The results of the study reveal that the width of the fetal zone of the adrenal gland presents much higher values in the case of patients with symptoms of premature birth, respectively an average value of 2,436 mm compared to 1,860 mm in the case of the control group.

7.4 Discussions

Our research showed that the best predictor of the risk of preterm birth within 7 days is the width of the fetal zone of the adrenal gland, having a predictive value of the cervical length.

In agreement, Turan's study also concluded that the size of the fetal area of the adrenal gland has a superior performance to the cervical length in identifying women at risk of preterm birth[4].

Chapter 8. Conclusions and personal contributions

In our research, the measurement of the transverse diameter of the thymus was possible for the patients with intrauterine growth restriction included in the study, and the results of our study were consistent with the data of previous studies, confirming the association between IUGR and reduced fetal thymus size.

Considering the importance of developing screening tools to identify women at risk of preterm birth, the last study proposed the ultrasound assessment of fetal adrenal gland size in pregnant women with symptoms of preterm labor, assuming that adrenal gland size can be an acute marker of premature birth.

Because there is no absolute definition of the effectiveness of preterm birth prediction or a category of the population where this prediction would be most appropriate, we also turned our attention to the evaluation of maternal characteristics, under different aspects of socioeconomic position. According to the results of the present study, we can state that the biometry of the fetal adrenal gland can be considered a predictor of premature birth.

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List of scientific journals

ISI Articles with impact factor

1. L Ples, V. Beliș, **A. Rîcu**, R. M. Sima” Medico-legal issues of the nuchal cord at birth” Journal of Romanian Legal Medicine 24(4)289-293(2016)DOI:10.4323/rjlm.2016.289
2. Liana Ples, Romina-Marina Sima, **Anca Rîcu**, Marius Moga, Cringu Ionescu "The efficacy of cervical cerclage combined with a pessary for the prevention of spontaneous preterm birth" Journal of Maternal Fetal & Neonatal Medicine doi.org/10.1080/14767058.2019.1670789

ISI Articles without impact factor (Proceeding of Congres)

1. Stanescu, AD ; Balalau, DO; Olaru, OG ; Balalau, C; **Ricu, AE** The Role of Ultrasound in Preoperative Diagnosis of Adnexal Tumors.THE ROMANIAN CONGRESS OF THE ROMANIAN SOCIETY OF ULTRASOUND IN OBSTETRICS AND GYNECOLOGY Pages: 560-565 Published: 2017
2. Pleş Liana, Carp Delia, **Ricu Anca**, Olaru Octavian Gabriel, Poenaru Mircea Octavian, Sima Romina-Marina. Atypical Presentation of Adenomyosis – Case Report and Literature Review Proceedings of SOGR 2018, pg. 678-682 ISBN 978-88-85813-33-5
3. Poenaru Mircea Octavian, **Ricu Anca**, Braicu Flavia, Pleş Liana Discrepancy Between High-Grade Colposcopic Lesions and HPV Negative 123-127 Proceedings of the 20th World Congress Of 4th National Congress of HPV, The First Congress of The Society of Endometriosis and East-European Infertility 2018

BDI Articles

1. Rîcu, A., Sima, R., Roşu, G., Zygouropoulos, N., & Ionescu, C. (2024). FETAL ADRENAL GLAND SIZE AND PREDICTION OF PRETERM BIRTH. *Romanian Journal of Clinical Research*, 7(1). <https://doi.org/10.33695/rjcr.v7i1.240>
2. Rîcu, A., Sima, R., Roşu, G., Zygouropoulos, N., & Ionescu, C. (2024). ASSOCIATION BETWEEN FETAL THYMUS SIZE AND INTRAUTERINE GROWTH RESTRICTION. *Romanian Journal of Clinical Research*, 6(2). <https://doi.org/10.33695/rjcr.v6i2.241>
3. **Delia Carp, Denise Diaconescu, D.C. Badiu, A. Edu, Anca Ricu, Romina Sima, Liana Ples.** Abdominal Pain în Pregnancy: Acute Pancreatitis - A Case Report **Journal of Surgical Sciences Vol.3, No.4**, decembrie 2016 ISSN 2360-3038
4. Liana Pleş, **Anca Rîcu, Romina-Marina Sima, C.A. Ionescu.** Coarctation of the aorta în a fetus with 46, xy, inv (9)(p12,q13) karyotype following în vitro fertilization **Journal of Surgical Sciences Vol.3, No.3, July - September 2016** ISSN 2360-3038
5. Liana Ples, **Anca Rîcu**, Bogdan Stoica, Sorin Păun.Giant mezenteric fibromatosis - a case report ROJSP 2016, Vol. I (issue 2): E 81-89

6. Liana Pleș, Banescu, B., **Rîcu, A.**, Otobic, A., Sima, R.M. Challenging Situations în Gynaecological Laparoscopy - Case Report and Short Literature Review. Bulletin of Transilvania University of Brașov. VOL. 8 (57), No. 1 – 2015 Series VI - Medical Sciences, ISSN 2065-2216 (Print), ISSN 2065-2224
7. Liana Ples, Romina-Marina Sima, **Anca Rîcu**, Anca-Daniela Stănescu, „Tratamentul chirurgical laparoscopic în tumorile ovariene/Laparoscopic Management of Ovarian Tumors”. Ginecologia.ro, anul III, Supliment nr.2/2015. ISSN Online 2457-3566.

Studies at international and national congresses

1. Liana Ples, RM. Sima, **A. Rîcu**, I. Sosievici, C. Moisei. Schizophrenia And Recurrent Pregnancies Outcomes. European Congress of Perinatal Medicine Maastricht, 15-18 Iunie, 2016
3. S Paun, I Negoii, B Stoica, I Tanase, **A Rîcu**, M Beuran „Neoplazia ovariana in urgenta – Factori predictivi ai unei rezectii adecvate oncologic „- National Congress Of Surgery, Sinaia, Romania, May 21-24 2014 – oral presentation
4. S Paun, B Stoica, Tanase I, **Rîcu A**, Negoii I, Beuran M „, Factori predictivi de morbiditate si mortalitate in neoplazia ovariana” – National Congress Of Surgery, Sinaia, Romania, May 21-24 2014 – poster presentation
5. Beuran M, Stoica B, Tanase I, **Rîcu A**, Negoii I, Paun S „Neoplasmul de vezicula biliara – experienta ultimilor 5 ani a SCUB” - National Congress Of Surgery, Sinaia, Romania, May 21-24 2014 – oral presentation
6. S. Păun, I. Negoii, B. Stoica, I. Tănase, **Anca Rîcu**, B. Popa, M. BeuranS „Hepatectomie stângă reglată pentru hemangiom cavernos gigant de lob stâng hepatic” – National Congress Of Surgery, Sinaia, Romania, May 21-24 2014 – poster presentation
7. S. Păun, I. Negoii, B. Stoica, **Anca Rîcu**, M. Beuran „Splenopancreatectomie corporeo-caudală pentru carcinom pancreatic” – National Congress Of Surgery, Sinaia, Romania, May 21-24 2014 – poster presentation

8. S. Păun, B. Stoica, I. Tanase, **Anca Rîcu**, M. Beuran „Massive intraoperative bleeding after laparoscopic assisted abdominoperineal resection”- National Congress Of Surgery, Sinaia, Romania, May 21-24 2014 – poster presentation
9. S. Păun, I. Negoii, I. Tănase, B. Stoica, **Anca Rîcu**, M. Beuran „Complicații trombotice tardive după cura chirurgicală laparoscopică a herniei”- National Congress Of Surgery, Sinaia, Romania, May 21-24 2014 – oral presentation
10. Ples L., Sina R., Moisei C., **Rîcu A.**, Stanescu A. – Genotipul Hpv in leziunile cervicale si distributia tulpinilor high risk in populatie – Prezentare Forum Ginecologia.ro 22-23 mai 2015, Bucuresti
11. Anca Daniela Stănescu, Romina-Marina Sima, **Anca Ricu**, Liana Pleș - Maternal hemodynamics in fetal growth restriction - Ginecologia.ro Nr 16 (2/2017)
12. Anca-Daniela Stănescu, Anca-Eugenia Ricu, Denisa-Oana Bălălaşu - The role of ultrasound in preoperative diagnosis of adnexal tumors - Ginecologia.ro Nr 16 (2/2017)
13. Impactul materno-fetal al consumului de droguri in timpul sarcinii – Liana Ples, Romina Sima, Delia Carp, **Anca Ricu**, Mircea Poenaru, Anca Stanescu – Ginecologia.ro Nr 15 (1/2017)

Summaries in journals at other international conferences

1. Delia Carp, Ionut Vâlcea, Romina-Marina Sima, **Anca Ricu**, Anca-Daniela Stanescu, Liana Pleș. Selective Intrauterine Growth Restriction in Multiple Pregnancies First Congress of Fetal and Neonatal Medicine, Londra 2017
2. Romina-Marina Sima, Ionut Vâlcea, **Ricu Anca**, Delia Carp, Anca-Daniela Stanescu, Liana Pleș. Choosing the optimal Way of Delivery for HBS Ag positive women. First Congress of Fetal and Neonatal Medicine, Londra 2017

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