UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA

DOCTORAL SCHOOL

Ph.D. THESIS
ABSTRACT

ULTRASONOGRAPHIC ASSESSMENT AND MONITORING OF THE INTRAUTERINE GROWTH RESTRICTION

PhD COORDINATOR

Professor CERNEA NICOLAE

PhD STUDENT

CĂTĂNESCU (NOVAC) MARIA VIOLETA

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INTRODUCTION

Restriction of fetal growth (IUGR) is one of the most important and complex issues in current obstetrics. It is well known that IUGR can lead to significant fetal or neonatal complications, both in the short and long term.

Monitoring fetal growth and fetal wellbeing is a major goal of prenatal care. Intrauterine growth restriction is a risk factor for a negative outcome progression including perinatal death, neonatal encephalopathy, childhood neurodevelopment deficiencies, and a range of adult diseases (20).

By defining the intrauterine growth restriction based on a certain threshold, for example, lower than the 10th percentile of estimated gestational weight (SGA- small for gestational age), this may probably not only result in the detection of fetuses with limited growth, but also to classify a group of "fetuses at risk" that are constitutionally small and healthy.

Typically, IUGR is a diagnosis that is established antenatally. However, especially for non-monitored pregnancy, the diagnosis is made in the neonatal period.

It is very important for obstetricians to recognize IUGR fetuses because this fetal condition is associated with an increase in perinatal morbidity, and mortality.

STATE OF KNOWLEDGE

CHAPTER I

EPIDEMIOLOGICAL DATA OF THE INTRAUTERINE GROWTH RESTRICTION

The "normal" newborn is one whose birth weight is between the 10th and 90th percentile as gestational age, sex and race, with no malnutrition and growth retardation.

In practice, when identifying an estimated fetal weight <10 percentile for gestational age, will monitor fetal growth and fetal physiology over time. A normal growth curve, normal Doppler velocimetry of the umbilical artery and normal amniotic fluid volume suggests a constitutional small fetus or minimal impact on the fetus due to uteroplacental insufficiency.

The term small for gestational age (SGA) is a non-IUGR entity but is also associated with a poor perinatal prognosis. SGA is defined as a birth weight under a certain percentile, usually percentile 10 for gestational age. The term IUGR should only be used for fetal development,

while SGA should be used especially in newborns, but can also be estimated from fetal ultrasound measurements (17).

The increased incidence of intrauterine growth restriction in the general obstetric population (10% - 15%) and decreased recognition during pregnancy (<40%) lead to increased perinatal morbidity and mortality.

Restricted fetuses, undetected during pregnancy are at increased risk, with a further doubling in the risk of stillbirth. 14 to 20 million newborns are affected annually by IUGR in developing countries. High rates of IUGR fetuses should be a cause of the alarm, not only indicating a risk of malnutrition and morbidity in women of childbearing age, but also a sign of high risk of malnutrition, morbidity, and mortality for newborns in developing countries (5).

Perinatal mortality corrected in the entire population of restricted fetuses <10 percentiles is 17.8 per 1,000 live births (2).

Currently, there are no specific therapies for IUGR treatment, and antenatal management refers to determining the ideal time and the way of birth. Prevention of complications associated with IUGR involves first establishing the diagnosis and then establishing appropriate supervision for the evaluation of fetal well-being followed by an appropriate intervention in case of fetal distress.

CHAPTER II

ETIOLOGY AND PHYSIOPATHOLOGY OF INTRAUTERINE GROWTH RESTRICTION

IUGR is due to a pathological slowdown in the growth rate of the fetus so that the fetus is unable to reach its growth potential. Causes of IUGR are generally described as being part of three main categories: maternal, fetal and placental. It is important that the etiologic factors in the IUGR are identified, as this also leads to an early diagnosis.

Genetic factors in IUGR. Hereditary thrombophilia, such as Leiden factor V mutations, prothrombin and methyltetrahydrofolate reductase (MTHFR); gene detoxification enzyme (CYP1A1) gene polymorphisms; growth factors (insulin-like growth factor-I); and hormones such as angiotensinogen are involved in the pathogenesis of fetal growth restriction.

Placental factors in IUGR. Placental insufficiency accounts for most IUGR cases and may affect up to 3% or more of all pregnancies. A single umbilical artery and velamentous umbilical cord insertion may also lead to a growth restriction.

Fetal factors in IUGR. Genetic causes can contribute to 5-20% of IUGR, especially in the case of early growth restriction fetuses (4). Congenital malformations are associated with IUGR, such as congenital heart disease, diaphragmatic hernia, omphalocele, gastroschisis, renal agenesia or dysplasia, anencephaly and single umbilical artery (16). More frequent infections including viral (rubella, CMV, herpes, varicella, herpes zoster, HIV) and parasitical (toxoplasmosis, syphilis, malaria) represent less than 5% of IUGR fetuses (12).

Maternal factors in IUGR. Several risk factors, environmental and behavioral factors that determine IUGR are known. These maternal causes are usually related to the reduction of uteroplacental blood flow, reduction of oxygen transport capacity or decrease in nutrition to the fetus (12).

CHAPTER III

DIAGNOSTIC CRITERIA OF INTRAUTERINE GROWTH RESTRICTION

Diagnosis of fetal growth restriction is currently performed based on an estimated weight of the fetus below a certain threshold, most often below 10 percentiles. It is likely that this definition does not have a high degree of sensitivity so as to miss growth restriction cases, not below the tenth percentile, but identifies a subgroup of high-risk pregnancies.

Screening and ultrasound diagnosis. There is a general consensus that once the IUGR has been suspected because of risk factors or physical examination, ultrasound techniques should be used to try to confirm or exclude the diagnosis. The necessary investigation for mother at increased risk of IUGR fetus includes assessment of the maternal and family history risk factor, maternal anthropometry with pre-pregnancy weight and maternal height, maternal nutrition status, exact date of gestation age, uterine height with palpation, fetal Doppler ultrasound and accurate fetal weight measurement, estimated by biometric measurements: abdominal circumference [AC], femoral head [HC] circumference, biparietal diameter [BPD] and femur length [FL] (8).

Doppler ultrasound. Doppler velocimetry is a non-invasive technique for assessing blood flow by downstream impedance characterization. The assessment of placental and fetal Doppler

blood flow has significantly changed IUGR management. The Doppler is used to determine vascular resistance and organ function.

Uterine artery Doppler. It has been shown that uterine artery Doppler in the third trimester may have a clinical value. Recent findings suggest that uterine artery Doppler in the third trimester was significantly associated with the risk of perinatal mortality (15).

Fetal Doppler. Doppler Umbilical artery (UA) impedance evaluation, middle cerebral artery (MCA) and ratio of pulsatility index to these vessels or cerebrovascular ratio (CPR) are used to assess fetal oxygenation. Umbilical artery Doppler is the only method that provides both diagnostic and prognostic information for IUGR management (25). Umbilical artery flow determines different degrees of affected placental function. The absent or reversed end-diastolic flow indicates a significant reduction in blood flow and serious damage to the fetus. A chronic hypoxia causes a redistribution of the fetal blood flow that manifests as vasodilatation in the brain. Cerebral vasodilatation, readily detectable as a reduction in PI of the middle cerebral artery, is an adaptive mechanism in response to hypoxia. This redistribution of blood flow, known as a brain-sparing reflex, is characterized by an increased rate of final diastolic flow (reflected by a low PI) in the middle cerebral artery (10).

CHAPTER IV

MANAGEMENT OF INTRAUTERINE GROWTH RESTRICTION

The antenatal detection rate of the IUGR is particularly low, considering that currently only one-third of such pregnancies are recognized prenatally (7).

Exact dating is the most important step in the prenatal management of the IUGR fetus, so in the first trimester, a very accurate measurement, the craniocaudal length, is used to estimate gestational age. The ultrasound determination of the cranial circumference, biparietal diameter, femur length, and abdominal circumference can be used to obtain an estimated weight using any of the available formulas.

Growth Restriction Intervention Trial found that among fetuses with early IUGR, long-term neurologic morbidity was improved for pregnancies where the birth was delayed as long as possible even though perinatal mortality was not altered (26).

The antenatal surveillance methods include cardiotocography, a biophysical score of the profile (tonus, movement, respiration and amniotic fluid index) and fetal arterial and venous

Doppler studies. These combinations, known as fetal integrated tests, allow for the most accurate assessment of the fetus wellbeing.

In the absence of any effective therapy, the primary role of IUGR management is an adequate control and timely delivery.

PERSONAL CONTRIBUTIONS

CHAPTER V

RESULTS OF THE CLINICAL STUDY AND STATISTICAL ANALYSIS

We conducted a prospective study that included a group of 157 pregnant women studied between October 2015 and December 2017. The study was conducted in the Obstetrics and Gynecology Clinic of the Municipal Clinical Hospital of Craiova and in the Center for Microscopic and Immunological Morphology Studies of the University of Medicine and Pharmacy Craiova.

During this period, patients were entered into the study by completing an initial assessment form and consent, following an investigation protocol that required the set of specific parameters measurable for the proposed study. The data collected in 126 IUGR single pregnancies were compared with those collected in 31 similarly selected single pregnancies that had intrauterine fetal growth corresponding to gestational age.

In terms of known risk factors that may be involved in IUGR, we considered that maternal age, parity, smoking, RCIU history, thrombophilia were not statistically significant ($p>0.05$) in our study. Only body mass index (BMI) showed a statistically significant correlation, $p <0.05$, which shows that maternal weight can influence the occurrence of RCIU, this being in line with the literature.

Regarding the pathology associated with the current pregnancy, we considered that diabetes mellitus, gestational diabetes and gestational hypertension were not statistically significant ($p> 0.05$) in our study, so they did not influence the occurrence of severe growth restriction (birth weight <10 percentiles). In contrast, the presence of preeclampsia showed a statistically significant correlation ($p <0.05$).

During pregnancy, we performed 2 ultrasound examinations, the first examination in the second trimester, at 19.6-23.6 weeks of pregnancy, and in the third trimester at 30.6-32.6 weeks

of pregnancy. In the second trimester, we also calculated the estimated fetal weight to see the development of the fetus. In the study group, we met 3 cases (2.38%) who had an EFW <10 percentiles, cases that have evolved with severe restriction until birth. We also met 8 cases (6.35%) who presented an EFW between 50-90 percentiles, but they have developed with a late growth restriction and at birth the newborn's weight was <10 percentiles. In the third trimester at 30.6-32.6 weeks of pregnancy, when we performed fetal morphology in both groups, we had an EFW of 1000-1500 gr in most cases, 84 cases (66.67%), compared to only 2 cases (6.45 %) in the control group. We noticed that EFW in the third trimester is statistically significant ($p < 0.05$), concluding that EFW in the second trimester and the beginning of the third trimester is correlated with the presence of severe growth restriction at birth.

Generally, gestational age at birth is <37 weeks due to complications that may occur and compromise fetal viability, which induces the premature birth with all the risks arising from this condition. By the Student t-test, we demonstrated that there is a significant difference between the mean gestational age at birth for the study group and those in the control group, those in the study group hase a much lower average than the others ($p < 0.001$).

The statistical correlation between the weight of the newborn and its sex showed that within each group there are no differences between male and female newborns, $p > 0.005$, although between lots there are significant differences between newborns of the same sex ($p<0.001$).

Using the Student t-test, we have shown that there is a significant difference between the mean placental weight of the study group and the control group, the cases in the study group being much lower than the others ($p < 0.001$).

Also, placental weight is closely related to the evolution of the fetus, and in our study, we correlate this parameter with the cerebroplacental ratio (CPR). Using the ANOVA test, we found that there were significant differences between the average placental weights calculated for the two groups, after the CPR division, p ANOVA <0.001. This shows that an average placental weight of 364.01 g there may be a decrease in CPR <1.

The unfavorable progression of the newborn was considered to be an Apgar score < 7 to 1 and 5 minutes and admission to the Department of Neonatal Intensive Therapy. We observed that for Apgar score, this is statistically significant, $p < 0.05$, so we have found a significant difference in the Apgar score in the two study groups and the IUGR. We also noticed a

significant difference ($p < 0.05$) between the Apgar score at 1 minute and abnormal Doppler on the uterine artery, umbilical artery and middle cerebral artery in the third trimester. Regarding admission to the Department of Neonatal Intensive Therapy, we found that this parameter is statistically significant, $p < 0.05$, so we objected a significant difference regarding the admission in the Department of Neonatal Intensive Therapy to the two groups of study and IUGR.

CHAPTER VI

ULTRASONOGRAPHIC PARAMETERS OF THE INTRAUTERINE GROWTH RESTRICTION

Precise dating of gestational age is extremely important since accurate knowledge of gestational age is critical for diagnosing IUGR. In our study, ultrasound dating of gestational age was performed in 80.95% of cases from the first trimester and only in 19.04% of cases in the second trimester.

Measurement of abdominal circumference (AC) seems to be much more predictive of IUGR than measuring either the circumference of the head or the biparietal diameter or the AC combination with either of these two variables. We found that this parameter, the AC percentile, was statistically significant, $p<0.05$, so we have found a significant difference between the AC percentile and the percentile at birth of the newborns in the two study groups.

In addition to the biometric assessment, Doppler deterioration models have been described in IUGR fetuses.

We found that the presence of abnormal Doppler velocimetry on the uterine artery in the second trimester was not statistically significant, $p>0.05$, so we did not find a significant difference between this parameter and the adverse outcome of newborns. Also, the accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) did not have a significant predictive value.

In the third trimester, the Doppler changes in the uterine artery increased in number, with an increase in IR> 0.65 with/without notch and S/D>3 being more evident. We found that this parameter was statistically significant, $p < 0.05$, so we have found a significant difference in the presence of abnormal Doppler velocimetry on the uterine artery in the third trimester and the adverse outcome of newborns. Accuracy, sensitivity, specificity, PPV, and PNV had significant predictive value. As a practical utility, we can say that Doppler changes in the uterine artery in the third trimester may be an independent predictor of fetal compromise.

In the second trimester of pregnancy, over the period 19.6-23.6 weeks, we have not experienced changes in Doppler velocimetry in the umbilical artery.

When 30% of villous vasculature ceases to work, an increase in umbilical artery resistance leads to a reduction in diastolic flow, pulsatility index> 95 percentiles. The presence of UA-IP>95 percentiles is statistically significant, $p < 0.05$, so we have found a significant difference in the presence of Doppler velocimetry on the UA, which showed IP> 95 percentiles in the third trimester and adverse outcome of newborns.

Accuracy, sensitivity, specificity, PPV, and PNV had significant predictive value. As a practical utility, we can say that the presence of AO-IP> 95 percentiles in the third trimester may be an independent predictor of fetal compromise, which should be taken into account when such cases require proper monitoring.

The predictive efficacy (Ac, Sn, Sp, PPV, PNV) of absent/reversal umbilical artery end-diastolic flow in the third trimester on newborn development was moderately significant, so it can not be an independent predictor of fetal compromise.

The presence of a UA abnormal Doppler in the third trimester of pregnancy is statistically significant, $p < 0.05$, so we have found a significant difference in the presence of an abnormal flow of UA and adverse outcome in newborns.

The predictive efficacy (Ac, Sn, Sp, PPV, PNV) of an abnormal UA Doppler in the third trimester of pregnancy have a significant predictive value for prediction of fetal compromise.

We noticed in the second trimester a relatively normal Doppler velocimetry in the middle cerebral artery, with IR, IP and S/D values within approximately normal limits, having mean IR values of 0.78 ± 0.033 SD, IP of 1.83 ± 0.088 SD and S/D 5.91 ± 0.342 SD.

In the third trimester of pregnancy, mean Doppler velocity values did not fall within the cut-off values, but absolute values showed that Doppler changes at the MCA level progressively degraded to IUGR fetuses. We met 25.39% of MCA-PI values <5 percentiles, indicating that there could have been brain-sparing changes in these cases.

The presence of an abnormal MCA Doppler in the third trimester is statistically significant, $p < 0.05$, so we have found a significant difference in the presence of abnormal flow on MCA and adverse outcomes of newborns.

The predictive efficacy (Ac, Sn, Sp, PPV, PNV) of the abnormal MCA-Doppler in the third trimester of the newborn progression had a significant predictive value.

The cerebroplacental ratio (CPR) quantifies the redistribution of cardiac output by dividing the Doppler indices from the two representative vessels, the middle cerebral artery, and the umbilical artery. This parameter, the presence of CPR <1 in the third trimester, is statistically significant, $p < 0.05$, so we have found a significant difference in the presence of CPR <1 and the unfavorable progression of the newborn.

The predictive efficacy (Ac, Sn, Sp, PPV, PNV) of CPR <1 in the third trimester of the newborn assessment had a significant predictive value, so it can be an independent predictor of fetal compromise.

CHAPTER VII

HISTOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY OF THE PLACENTA IN THE RESTRICTION OF GROWTH

The relationship between the Doppler models of the umbilical and middle cerebral artery in IUGR and placental pathology is easier when the most severe models are present, absent end-diastolic flow or reversed end-diastolic flow.

Histological study of IUGR placenta. The histological findings showed to have significant proportions in IUGR placenta compared to normal placenta, we considered it could contribute to the development of IUGR: peri and intervillous fibrinoid necrosis, inter/intra/perivillous syncytial knots, vascular stasis, intravillous microcalcifications with areas of villous necrobiosis, placental infarction over 5%, stem villi with dilated vessels, some with stasis, others with thrombosis, placental villi with pseudo-angiomatous dilated vessels, or chorangiosis.

The association between the presence of syncytial knots, showing a repeated and long-lasting syncytiotrophoblast injury and the presence of the chorangiosis aspect, indicating a vascular adaptation of chronic hypoxia, is associated with the presence of IUGR. We considered that this association was specific to vascular hypoxia, and could be characteristic of severely restricted intrauterine growth. Fibrinoid necrosis, stromal fibrosis, and obstructive vasculopathy were seen only in IUGR placentas. In the present study, we found an increase in syncytial knots, which were more common in the IUGR placentas compared to normal placentas (26.69% vs 9%). The histological analysis showed that the onset of lesions was triggered at the level of stem villi, more quantitative than qualitative changes in the placental structure resulting in functional changes, that are involved in this pathology of pregnancy.

Immunohistochemical study of IUGR placenta. Angiogenesis plays an important role in the development of a new vascularization from pre-existing blood vessels and the completion of terminal villi in the placenta. In our study, we used the following IHC markers: CD31 (platelet endothelial cell adhesion molecule (PECAM-1) also known as differentiation cluster 31), CD34 (a transmembrane phosphoglycoprotein protein encoded by the CD34 gene also known as differentiation cluster 34), Vascular endothelial growth factor (VEGF) is a signal protein produced by cells that stimulate blood vessel formation, eNOS (Endothelial nitric oxide synthase - an enzyme which is encoded by the NOS3 gene in humans, is one of three isoforms which synthesizes nitric oxide (NO), which plays an essential role in regulating vascular tone, cell proliferation, leukocyte adhesion and platelet aggregation.

VEGF expression was identified at syncytiotrophroblast and extravillous trophoblast in the mature placenta. His immunoreaction was strongly positive at the syncytiotrophoblast level in stem villi, mature intermediate villi, and even at the level of syncytial knots.

We noticed an intense *eNOS* immunoreaction at the arteriolar tunica media of the stem villi with a progressive decrease in intensity at mature intermediate villi and terminal villi.

CD31 immunoreaction was strongly positive on vascular endothelium at stem villi, mature intermediate villi, terminal villi.

Expression of *CD34* immunoreactivity was lower in capillary endothelial cells of villi as well as in trophoblastic cells from IUGR group than in normal pregnancies.

GENERAL CONCLUSIONS

- In terms of known risk factors that may be involved in IUGR, we considered that maternal age, parity, smoking, IUGR history, thrombophilia were not statistically significant ($p>0.05$) in our study. Only body mass index (BMI) showed a statistically significant correlation, $p <0.05$
- Regarding the pathology associated with the current pregnancy, we considered that diabetes mellitus, gestational diabetes and gestational hypertension were not statistically significant ($p> 0.05$) in our study, so they did not influence the occurrence of severe growth restriction (birth weight <10 percentiles). In

contrast, the presence of preeclampsia showed a statistically significant correlation ($p < 0.05$).

- We have noticed that EFW in the 2nd and 3rd trimesters is statistically significant ($p < 0.05$), saying that EFW in the second trimester and the beginning of the third trimester is correlated with the presence of severe growth restriction at birth.
- Using the Student t-test, we have shown that there is a significant difference between the average placental weight of the study group and the control group, the cases in the study group being much lower than the others ($p < 0.001$).
- By performing the ANOVA test to correlate the placental weight to the newborn, we found that there were significant differences between the average placental weights calculated for the two groups after the CPR division, p ANOVA <0.001. This shows that an average placental weight of 364.01 g there may be a decrease in CPR <1.
- Doppler changes in the uterine artery in the third-trimester show statistically significant differences, $p < 0.05$, in the presence of abnormal Doppler velocimetry on the uterine artery in the third-trimester and adverse outcome of newborns.
- Accuracy, sensitivity, specificity, PPV, and PNV had a significant predictive value, so Doppler changes in the uterine artery in the third trimester may be an independent predictor of fetal compromise.
- The presence of UA-PI> 95 percentiles is statistically significant, $p < 0.05$, so we showed a significant difference in the presence of Doppler velocimetry on UA that showed IP> 95 percentiles in the third trimester and adverse outcome of newborns.
- Accuracy, sensitivity, specificity, PPV, and PNV had a significant predictive value, so the presence of UA-PI> 95 percentiles in the third trimester may be an independent predictor of fetal compromise.
- The presence of an abnormal Doppler on MCA in the third trimester is statistically significant, $p < 0.05$, so the predictive efficacy (Ac, Sn, Sp, PPV, PNV) of abnormal MCA-Doppler in the third-trimester of newborn progression had a significant predictive value.

- The presence of CPR <1 in the third trimester is statistically significant, p <0.05, so predictive efficacy (Ac, Sn, Sp, PPV, PNV) had a significant predictive value, so it can be an independent predictor of fetal compromise.
- Histological analysis showed that the onset of lesions was triggered at the level of stem villi, with a characteristic association of syncytial knots with a pseudo-angiomatous aspect, more quantitative than qualitative changes of the placental structure resulting in functional changes that are involved in this pathology pregnancy.
- eNOS immunoreaction was strongly positive at the arteriolar tunica media of stem villi with a progressive decrease in intensity at mature intermediate villi and terminal villi.
- VEGF immunoreactivity was strongly positive in syncytiotrophoblast from stem villi, mature intermediate villi, and even at the level of syncytial knots.
- CD31 immunoreaction was strongly positive on vascular endothelium at stem villi, mature intermediate villi, terminal villi.
- Expression of CD34 immunoreactivity was lower in capillary endothelial cells of villi, as well as in placental trophoblastic cells in IUGR pregnancies than in normal pregnancies.

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