

**VICTOR BABEȘ UNIVERSITY OF MEDICINE  
AND PHARMACY TIMIȘOARA  
FACULTY OF MEDICINE  
DEPARTMENT OF OBSTETRICS-GYNECOLOGY**

**MIHAELA NARCISA NICOLAU (ȚUNESCU)**



# **PHD THESIS**

**CONSIDERATIONS ON NEONATAL OUTCOME  
IN PRETERM NEONATES WITH INTRAUTERINE  
GROWTH RESTRICTION**

## **A B S T R A C T**

Scientific Coordinator

**ASSOC. PROF. BERNAD ELENA SILVIA, MD PhD**

<b>PROF. CONSTANTIN ILIE, MD PhD</b>
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# 1. INTRODUCTION – MOTIVATION OF THE STUDY

The doctoral study completed with the thesis entitled "Considerations on neonatal outcome in preterm neonates with intrauterine growth restriction (IUGR)", coordinated by Prof. Univ. Dr Constantin Ilie, was carried out in the Neonatology Department – NICU, Odobescu Maternity – Emergency Municipal Clinical Hospital Timisoara and in the Timisoara County Emergency Clinical Hospital "Pius Branzeu". The experience gained in Neonatal Intensive Care, the rising number of extremely low birth weight infants surviving in modern neonatal therapies, as well as the therapy of a highly vulnerable category - the intrauterine growth-restricted preterm infant - has led me to become more involved in the effort to find the optimal time of extraction of a preterm fetus with IUGR - taking into account antenatally obtained Doppler parameters. Moreover, try to minimize the early neonatal consequences as much as possible.

The objectives of the study are dictated by a significant preoccupation in the field both in Romania and in the world; existing studies show that IUGR is a critical health problem in developing countries around the world, being one of the "great obstetric syndromes" associated with placental defects but also one of the topical problems of neonatology and in particular the association between IUGR and prematurity below 32 weeks gestational age. Neonatal morbidity and mortality are significant, and the economic impact is imperative. It is, therefore, clear that stricter diagnostic criteria are needed.

This study aims to highlight the importance of interdisciplinary collaboration regarding the specific pathology of the preterm newborn with IUGR: obstetrician, neonatologist, geneticist, cardiologist, neurologist, physiotherapist, and family physician. The results of this study will provide information on the importance of dispensing pregnancy and diagnosing pregnancy with additional risk. Furthermore, informing the future mother about the risks of prematurity and association with IUGR and the development of a pre-and postnatal monitoring sheet will attempt to find the optimal time of extraction of the premature newborn with IUGR.

Fetal growth restriction remains challenging due to difficulties in achieving a definitive diagnosis and management. Intrauterine growth restriction is associated with an increased risk of perinatal mortality and morbidity, as well as with a poor long-term outcome.

On 11 March 2020, the World Health Organization declares a pandemic and introduces the disease called COVID-19. The limited research on the impact of the new Coronavirus on the prenatal period, delivery as well as postnatal period, as well as insufficient data on the transmission of the virus from the sick mother to the fetus during intrauterine life was also a concern for us during 2020, when the activity in our maternity ward was restricted, with only emergencies being provided. Following the protocol

implemented by health institutions to prevent the transmission of the SARS-CoV-2 virus, all pregnant women who tested positive for COVID-19 were referred to the Emergency Clinical County Hospital of Timisoara - Bega Maternity Hospital (declared a COVID maternity hospital). Our study was limited by the small number of cases and followed the effects of SARS-CoV2 infection on the pregnant woman, on the evolution of the pregnancy and on the way the pregnancy was completed. The development of agreed protocols for the clinical and quasi-clinical management of newborns of SARS-CoV-2 positive mothers continues to remain a concern and may continue to lead to important findings.

## **2. AIM AND OBJECTIVES OF THE RESEARCH**

Despite numerous attempts to manage fetal growth restriction, there are still no effective treatments to improve fetal growth.

Fetal growth restriction continues to be associated with increased perinatal mortality and morbidity and a poor long-term prognosis in terms of complications such as poor neurological development, type II diabetes mellitus and arterial hypertension.

Gestational age is the most significant determinant of morbidity and survival in this category of newborns, intending to find the optimal extraction time of a preterm infant with gestational age below 32 weeks with IUGR.

### **The present study has the following main objectives:**

1. To improve the means of diagnosis and thorough monitoring of pregnancies at risk of preterm birth with IUGR.
2. Identify pre- or post-natal factors commonly associated with prematurity under 32 weeks and early IUGR that may be a warning signal for the development of complications.
3. Use of non-invasive methods for the detection of brain and splanchnic distress (cranial ultrasound, NIRS) early postnatal to avoid occurrence of severe complications and to modify some current medical practices following the obtained data in order to reduce the incidence and severity of complications in this category of newborns.
4. Correct diagnosis of IUGR and forms of IUGR
5. Find the optimal time of delivery of the preterm infant with IUGR so that early neonatal consequences are minimized, by calculating HI taking into account RPC within 3-5 days. Establish a reference value for HI.

6. An analysis of the general characteristics and pregnancy outcome of COVID-19 patients in 2020

### 3. TYPE OF STUDY

The personal study presented in this paper (studies 1-6) prospective study conducted for 6 years, January 2016 - December 2020, in the Neonatology Department - Neonatal Intensive Care – and in the Obstetric-Gynecology I and II Department of Odobescu Maternity Hospital of the Municipal Emergency Hospital Timișoara. Data was collected from the patients' charts (pregnant woman and neonates) and filled up with data from National Registry of Respiratory Distress of Romania. The total lot contains 618 preterm newborns with GA under 32 weeks, further subdivided into AGA preterm with GA under 32 weeks (398) and IUGR preterm with GA under 32 weeks (220). IUGR preterm infants were further divided according to the presence or absence of centralization of circulation.

Inclusion criteria:

- Preterm with IUGR with gestational age below 32 weeks
- Preterm AGA with gestational age under 32 weeks
- Born in the Odobescu Maternity Hospital of the Timișoara - Clinical Municipal Emergency Hospital.
- Born in other maternity and brought by transfer
- Gestational age under 32 weeks
- Common short-term morbidities:
  - Respiratory Distress Syndrome
  - Apnea of prematurity
  - Severe thrombocytopenia
  - Paralytic ileus/ spontaneous intestinal perforation
  - Intraventricular hemorrhage
  - Anemia of prematurity
- Common medium-term morbidities:
  - Chronic lung disease
  - Retinopathy of prematurity
  - Necrotizing enterocolitis
- HI  $\geq 85$ , CPR  $\leq 1,1$
- NIRS cerebral and somatic – rsO<sub>2</sub> cerebral  $> 50$  or  $< 50$ , rsO<sub>2</sub> splanchnic  $< 50$
- RI on ACA via Doppler ultrasound  $< 0,65$  vs.  $> 0,65$

Study 7 was carried out during 2020 in the Neonatal Intensive Care Unit as well as in the Obstetrics - Gynaecology I and II Unit of the Odobescu Maternity Hospital - Municipal Emergency Clinical Hospital Timișoara as well as in the Obstetrics - Gynaecology I and II Clinical Units and the Neonatology Unit of the "Pius Brânzeu" County Emergency Clinical Hospital Timisoara. This study aimed to analyze the general characteristics and pregnancy outcome in patients with COVID-19. The study included pregnant women who were diagnosed positive for SARS-CoV2, admitted in the Municipal Emergency Clinical Hospital Timișoara in 2020. All pregnant women admitted in our maternity hospital in 2020 (although our maternity hospital was not a COVID-supporting maternity hospital during this period) regardless of GA were included in the study. The group of pregnant women in whom the diagnosis of pregnancy and the presence of SARS-CoV2 infection was established was of 149 eligible patients.

**Inclusion criteria:**

- Pregnant women with the diagnosis of pregnancy and the presence of SARS-CoV2 infection, admitted in the Municipal Emergency Clinical Hospital Timișoara and "Pius Brânzeu" County Emergency Clinical Hospital Timisoara in year 2020
- Newborn delivered to mothers with SARS-CoV-2 infection independent of GA

**Exclusion criteria:**

- Women not diagnosed with pregnancy and SARS-CoV-2 infection admitted to Municipal Emergency Clinical Hospital Timișoara in 2020
- Newborns born to mothers negative for SARS-CoV-2 regardless of GA

## **4. METHOD**

**Studies 1-6**

The clinical assessment of preterm infants with GA < 32 weeks and IUGR followed the following steps:

1. Conduct information and obtain informed consent
2. Indication for elective cesarean delivery was a decision of both obstetrician and neonatologist where Doppler measurements and follow-up of pregnancy progress with early IUGR were performed. Late decelerations, absence of fetal weight gain with progressive oligohydramnios on 2 successive biweekly ultrasound scans, pre-eclampsia and occurrence of reversed end-diastolic flow in the AO necessitated cesarean section delivery. HI was calculated based on the last 3-5 CPR measured in



the last 3-5 days prior to delivery. On days excluded from the study, the CPR value was determined as the mean value of the two closest values measured over a 48-hour interval. After birth, HI was calculated by adding the daily reductions of CPR (per cent below the cut-off value of 1) over the observation period. At CPR values below 1 with progressive decrease and the appearance of the phenomenon of centralization of circulation as well as HI 80-85, it was decided to deliver the fetus.

3. The first examination is done at birth to establish the diagnosis of preterm with IUGR based on LMP, clinical evaluation, Ballard score, and selection of patients according to the inclusion criteria.
4. For the determination of GA and nutritional status, we used LMP and Ballard score.
5. Cerebral ultrasound and determination of RI on cerebral arteries – ACA, (RI on ACA secondary to centralization of circulation is  $<0,65$ , and at IUGR preterm without centralization of circulation is  $>0,65$ ) associated with NIRS monitoring in the first 24-72 hours of life. Normal values for cerebral rsO<sub>2</sub> is 58 – 80 and for splanchnic 70 – 90. Decreasing by 20% below base line or under 50 is cause for concern. These values of cerebral or somatic oxygenations are expressed as percentages.
6. Monitoring and treatment of early and mid-term neonatal complications
7. For each individual case a protocol was drawn up containing data that we entered in a form that we personally designed (Appendix 4). This monitoring chart consists of important maternal data: pregnancy monitoring, performed ultrasound, preexisting or associated pathologies, antenatal diagnosis of early or late IUGR based on Doppler measurements, CPR in a period 3-5 days and HI determined by neonatologist. Neonatal data are birth weight, GA, resuscitation in the delivery room, Apgar score at 1/5/10 minute, determination of IUGR type, cranial ultrasound, NIRS, associated pathologies and their treatment.

## **Study 7**

For study 7 the diagnosis of SARS- CoV2 infection was established by collecting nasopharyngeal exudate from pregnant women who presented to the emergency department and were then admitted. According to the procedure in force at that time, pregnant women detected positive were transferred to the "Pius Brinzeu" Timisoara Emergency Clinical County Hospital (SCJUPBT), where medical care continued until discharge. Therefore, the present study included both the patients transferred from the SMUT and the other pregnant or lactating women admitted to the SCJUPBT during the study period.

## 5. RESULTS

### STUDY 1 – DESCRIPTIVE CHARACTERISTICS OF THE TOTAL GROUP OF PREGNANT WOMEN AND PRETERM INFANTS WITH GA UNDER 32 WEEKS

**Aim:** to analyze maternal and neonatal factors in the total group of IUGR preterm infants with a VL under 32 weeks

**Material și method.** The study was prospective and maternal and neonatal data were collected from observation sheets. For these lots we analyzed maternal and neonatal factors.

#### 1.a. Descriptive characteristics of the total group of pregnant women

Total lot of pregnant women is of 618 and the results were analyzed based on: maternal age, nutritional status at birth, type of pregnancy - single or multiple, type of birth, mode of obtaining the pregnancy, type of birth, corticosteroid therapy, type of cure - complete/incomplete, pregnancy complications.

**Results:** Related to maternal age, the majority of cases were young with age between 18-30 years (328 /53.07%), singleton pregnancy (516 /83.5%), cesarean section (403 /65.2%) fetal indication for this method of delivery was high (403/65,2%) out of total of 618 patients. Naturally obtained pregnancies were 597/96.6% compared to in vitro fertilization 21/3,4%. Complete antenatal corticotherapy was administrated at 434/70.2% and incomplete cure at 72/11,7% of patients. A total of 173(28%) did not receive any corticosteroid therapy. A significant high number of pregnancy were complicated (554/ 95.2%).

#### 1.b. Descriptive characteristics of the total group of preterm infants with GA under 32 weeks

**Material:** Out of a total of 16337 infants born between 2016-2020, 618 newborns represent the study group – preterm with GA under 32 weeks, of which 498 were AGA preterms and 120 IUGR preterm. Main descriptive characteristics of preterm with GA under 32 weeks: GA, gender, birth weight, weight at discharge, ponderal index, postnatal age at which birth weight was achieved, duration of hospitalization (days), SpO2 from umbilical cord, used oxygen concentration, method of resuscitation, death and cause of death.

**Results:** Mean gestational age was  $29.57 \pm 2.3$ , with the predominance of female newborns 313 (50.6%), and a number of 478 (77,35%) needed resuscitation in the delivery room involving PPV + T piece resuscitator. A small number of this newborns needed prolonged resuscitation 43 (7.7%). Mean birth weight was  $1293.01 \pm 387.31$  and mean

discharge weight  $2182.49 \pm 677.86$ . Mean SpO<sub>2</sub> of umbilical cord sampling was 81.49 and mean oxygen concentration used in the delivery room  $51.99 \pm 20.45$  (Tabel 3, Figure 17,19).

Out of a total of 618 preterm newborns with GA under 32 weeks, 59 died (9.54%) with the main cause being infection (61,01%, respectively 36 de cases). Cerebral complications were registered in 23 cases (38,98%), while pulmonary in 6( 10,1%) ( Tabel 4)

**Conclusions:** Results of the analyze showed predominance of female gender and resuscitation need in the delivery room and the main cause of death was infectious.

## **STUDY 2 - DISTRIBUTION OF MATERNAL/NEONATAL VARIABLES IN THE 2 GROUPS COMPARED - AGA AND IUGR PRETERM INFANTS**

**Aim:** analyze of maternal and neonatal factors in the 2 subgroups: AGA and IUGR preterm infants

**Material și metodă.** In study 2, we divided the main lot of 618 preterm infants with GA under 32 weeks in AGA preterm (398) and IUGR preterm (220).

**Results:** No statistically significant differences between the two studied groups in terms of maternal variables were found: maternal age ( $p=0,34$ ), type of pregnancy (singleton/multiple) ( $p=0,26$ ), obtained pregnancy (natural/IVF)( $p=0,73$ ), type of delivery ( $p=0,09$ ), antenatal administration of corticotherapy ( $p=0,40$ ). Maternal mean age between 18-30 years was higher in the AGA preterm group compared to IUGR preterm (230/57,78% vs. 98/44,54%), without significant statistical value, as well as obtained pregnancy (natural/IVF) (382/ 95.94% vs. 209 /95.0 %) and indication of delivery (maternal vs fetal) (285/71.60% vs. 168 / 76.36%). With statistical significant value was complicated pregnancy – 11.35% in the IUGR preterm group compared to 4.1% in the AGA group ( $p=0.002$ ).(Table 5-6, Figure 20-28).

**Concluzii:** Comparing AGA preterm group with IUGR preterm group, higher incidence was found for maternal age, method of obtaining the pregnancy, antenatal corticotherapy, indication of delivery, but without statistical significant value. IUGR preterm lot has significant statistical value for pathologies associated with pregnancy – HTAIS, GDM, placental insufficiency – compared to AGA group where chorioamnionitis exceeded.

## **STUDY 3. CORRELATION OF DOPPLER CHANGES IN UMBILICAL ARTERIES, MIDDLE CEREBRAL ARTERY AND CEREBRO-PLACENTAL INDEX WITH HYPOXIA INDEX (IH) IN 3 TO 5 DAYS BEFORE BIRTH DEPENDING ON THE PRESENCE OR ABSENCE OF CENTRALIZATION OF CIRCULATION.**

**Aim:** determination of hypoxia index based on cerebro-placental index (CPR) obtained over a period of 3-5 days prior to delivery depending on the presence or absence of centralization of circulation in order to determine the decision to deliver an IUGR preterm

with GA under 32 weeks. Analyzing the cerebral and splanchnic complications in the presence of centralization of circulation.

**Material and method:** HI was calculated based on the last 3-5 CPR measured in the last 3-5 days prior to delivery. On days excluded from the study, the CPR value was determined as the mean value of the two closest values measured over a 48-hour interval. Based on CPR – 1.1 and HI 80-85 the decision to deliver the IUGR preterm fetus was assessed by neonatologist and obstetrician. (Table 8) Out of a total of 220 IUGR preterm, Doppler and CPR measurements were obtained at 152 pregnant women. Based on CPR values, HI was calculated. Cerebral – intraventricular hemorrhage graded by Papille classification, periventricular leukomalacia – and mesenteric complications – gastric residual, paralytic ileus, NEC - were considered.

**Results:** Based on the presence or absence of centralization of circulation, we found that out of 152 IUGR preterm, 82 presented centralization of circulation with progressive decrease in CPR and increase in HI -  $CPR \leq 1$ ,  $HI \geq 85$  at the time of delivery – progress monitored over 3 to 5 days and developed cerebral complications – IVH grade 2-3 (23 cases), periventricular leukomalacia grade 2-4 (12 cases) – and splanchnic complications, such as gastric residual/paralytic ileus (20 cases). These findings are statistical significant ( $p < 0.0001$ ) compared to IUGR preterm without centralization of circulation ( $CPR \geq 1$ ,  $HI \leq 85$ ), who developed less severe cerebral complications – IVH grade 1-2 (45 cases), PVL grade 1-2 (10 cases). Splanchnic complication were not present at the group without centralization of circulation. (Table 8).

**Conclusion:** once the centralization of circulation is installed with decreasing of  $CPR \leq 1$  and increasing of  $HI \geq 85$ , cerebral and splanchnic complications are severe (IVH grade 2 - 3, LPV grade 2 - 3 precum și NEC stage 1 - 2)

#### **STUDY 4. NONINVASIVE MONITORING OF CEREBRAL AND SPLANCHNIC OXYGENATION PERFORMED IMMEDIATELY AFTER BIRTH AT IUGR PRETERM NEWBORNS IN THE PRESENCE OR ABSENCE OF CENTRALIZATION OF CIRCULATION USING INFRARED SPECTROSCOPY (NIRS) AND DEPENDING ON GA**

**Aim:** improvement of the quality of early neonatal management by noninvasive monitoring of cerebral and splanchnic oxygenation in the presence of the phenomenon of centralization of circulation.

**Material and method:** we evaluated the state of cerebral and splanchnic oxygenation at the level of 152 newborns in which Doppler measurements were performed (RI calculation on ACA - below 0.65 as a result of the presence of the phenomenon of centralization of circulation) using NIRS infrared spectroscopy initiated in the first 24 hours after birth and maintained for 72-96 hours (Table 9). The sensors were placed on the

forehead for regional cerebral saturation (rSO<sub>2</sub>-cerebral) and on the subumbilical abdomen for regional splanchnic saturation (rSO<sub>2</sub>-mesenteric).

We have established as reference values of the regional cerebral saturation of oxygen - cerebral rsO<sub>2</sub> >50(%) and of the splanchnic regional saturation rsO<sub>2</sub>>50(%) in the 2-3 days of NIRS monitoring. These values are expressed as a percentage. rSO<sub>2</sub> measurements were made with INVOS 5100C (COVIDIEN, Mansfield, MA, USA) We compared developed complications by gestational age according to the presence or absence of the phenomenon of centralization of circulation.

**Rezultate:** Out of the group of 82 IUGR preterm infants who presented centralization of circulation, 49 had a cerebral rsO<sub>2</sub> >50, a gradual increase in the first hours after birth and a maintained value over 50. This group developed cerebral complications – intraventricular hemorrhage grade 1-2 (IVH grade 1 n = 26, IVH grade 2 n=23), while an rsO<sub>2</sub> <50 involved cerebral complications such as IVH 2-3 in a number of 23 cases and LPV degree 2-3 in a number of 10 cases. Splanchnic regional saturation - splanchnic rsO<sub>2</sub> < 50 resulted in paralytic ileus, NEC grade I/II in 23 cases.

IUGR preterm infants in which the presence of the phenomenon of centralization of circulation was not observed - cerebral rsO<sub>2</sub> >50 – did not developed significant cerebral complications. At those who had cerebral rsO<sub>2</sub> <50 cerebral complication such as intraventricular hemorrhage grade 1-2 (45 cases ) or LPV grade 1 (10 cases ) occurred, while splanchnic rsO<sub>2</sub> < 50 did not result in splanchnic damage. (Table 9).

Early IUGR preterm infants who showed centralization of circulation and HI >50 presented in a percentage of 9.75% IVH grade 2 in the GA group 24-26 weeks, 2.43% in the group 26-28 weeks, 12.19% in the group 28-30 weeks and 3.65% in the group of 30-32 weeks. The IUGR preterm who presented HI<50 in the presence of the centralization of circulation developed IVH grade 3 in a percentage of 12.19% in the group 24-26 weeks, 9.75% in the group 26-28 weeks , 3.05% in the group 28-30 weeks and 2.43% in the group 30-32 weeks. Cerebral complications of the type LPV grade 2 and 3 were recorded in the group of 24-28 weeks. The group without the centralization of circulation and with HI>50 had a lower incidence of minor complications, compared to those with HI<50 and in which the presence of IVH grade 2 is observed in a percentage of 14.28% in the group of VG 24-26 weeks, 4.28% in the group 26-28 weeks, 2.85 % in the group 28-30 weeks and 2.85 % in the group 30-32 weeks. The splanchnic saturations rsO<sub>2</sub> in the presence of the phenomenon of centralization of the circulation <50 had as consequences manifestations of the type: paralytic ileus in a higher percentage in the group 24-26 weeks compared to the other age groups.

**Conclusions:** Statistically significant (p<00,0001) IUGR preterm infants with the presence of the phenomenon of centralization of circulation and changes in regional cerebral

and / or splanchnic saturation have developed more severe cerebral or splanchnic complications Cerebral and splanchnic complications are all the more severe as the GA decreases.

## **STUDY 5 – DESCRIPTIVE CHARACTERISTICS OF THE GROUPS OF PRETERM NEWBORNS WITH GA UNDER 32 WEEKS – TOTAL AGA PRETERM/TOTAL IUGR PRETERM – COMPARATIVE GROUPS**

**Aim:** analyze of neonatal factors in the 2 groups: AGA vs IUGR preterms with GA under 32 weeks and of the early and mid-term complications developed in this categories of newborns.

**Material and method:** comparing the descriptive characteristics of the the groups of preterm infants with GA under 32 weeks – AGA preterm and IUGR preterm.

**Results:** No statistically significant differences were revealed regarding the gestational age (29,43/29,92,  $p=0,02$ ), gender ( $p=0,05$ ), birth weight (g)(1348,29/1124,48,  $p=0,05$ ), the weight at discharge (g) (2210,69/2106,53,  $p=0,09$ ) , the duration of hospitalization (days) (38,31/42,97, $p=0,09$ ), oxygen concentration used in the delivery room (54,16/52,24,  $p=0,34$ ). between the two lots. (Table 11, Figure 27-33). Statistically significant was the need of resuscitation in the delivery room higher in AGA preterm infants (330-82.91%) compared to RCIU preterm infants (92 - 41.81%) using PPV with a T piece resuscitator ( $p<0,0001$ ), as well as prolonged PPV + ECM resuscitation. (Table 11)

**Conclusions:** The premature AGA group required resuscitation at the delivery room which was statistically significant compared to the RCIU group, which is explained by the pulmonary immaturity.

## **STUDY 6 – EARLY AND LATE NEONATAL COMPLICATIONS OF PRETERM INFANTS WITH GA UNDER 32 WEEKS WITH IUGR DEPENDING ON THE PRESENCE OR ABSENCE OF CENTRALIZATION OF CIRCULATION**

**Aim:** analysis of early and late complications of premature RCIU in the presence or absence of the phenomenon of centralization of circulation.

**Material and method.** Depending on the presence or absence of the phenomenon of traffic centralization, in Table 13 we have shown the descriptive analysis of the 152 RCIU preterm infants with VG under 32 weeks at which CPR and HI were calculated.

**Results:** There were no statistically significant differences regarding the gestational age (28,43/28,72,  $p=0,02$ ), gender ( $p=0,22$ ), birth weight(g) (1348,29/1144,48,  $p=0,03$ ), the weight at discharge (g) (2210,69/2106,53,  $p=0,17$ ), the duration of hospitalization(days) (38,31/42,97,  $p=0,09$ ), oxygen concentration used in the delivery room (54,16/52,24,  $p=0,34$ ) between the two lots. The birth status of these IUGR preterm infants was evaluated by the

Apgar score at 5 min, with no statistically significant differences between the two sublots ( $p=0,01$ ). The need of resuscitation in the delivery room was without statistical significance depending on the method of resuscitation using PPV with a T piece resuscitator, PPV+ECM or PPV with bag and mask ( $p=0.17$ ). Statistically significant was the incidence of apnea of prematurity in the group of IUGR premature infants without the phenomenon of centralization, ( $p<0,0001$ ). Respiratory distress syndrome was significantly higher in the group of IUGR preterm infants who presented the phenomenon of centralization compared to the group without centralization of circulation ( $p\leq 0.001$ ).

Moderate and severe thrombocytopenia  $\leq 50.000/\text{mm}^3$  was statistically significant more frequent in the premature group with IUGR and the phenomenon of circulation centralization, in all 70 cases (100%,  $p<0.001$ ) thrombocytopenia was transitory although it was a severe or moderate form. Intraventricular hemorrhage, in varying degrees according to the Papille classification, was statistically significantly more common in the group of preterm infants with IUGR and the presence of the phenomenon of centralization of circulation ( $<0.001$ ). PDA had a higher incidence in the group of premature infants without circulation centralization (49 cases out of 82 vs. 22 cases out of 70 cases -  $p<0.001$ ).

Considering medium and late-term complications, no significant statistically differences were found between the groups regarding periventricular leukomalacia (Figure 46) and retinopathy of prematurity of different grades, while chronic lung disease had higher incidence at the preterms with IUGR and centralization of circulation with statistically significant values (55 vs. 12,  $p<0.001$ ), as well as NEC (20 cases,  $p<<0.001$ )

**Conclusions:** The occurrence of the phenomenon of centralization of circulation had as consequences in the IUGR group compared to the AGA group regarding early complications such as: thrombocytopenia, IVH grade 2-3, RDS and for medium- and late-term complications: NEC and CLD.

## **STUDY 7- ANALYSIS OF GENERAL CHARACTERISTICS AND OUTCOME OF PREGNANCY IN COVID-19 PATIENTS**

**Aim:** Study of the effects of SARS-CoV2 infection on the pregnant woman, on the evolution of pregnancy and on the outcome of pregnancy.

**Material and method:** The study included patients in whom the diagnosis of pregnancy was established, who have been diagnosed positive for SARS-CoV-2 infection, hospitalized in the Timisoara Municipal Emergency Clinical Hospital (SCMUT) in 2020. The diagnosis of SARS-CoV2 infection was established by collecting nasopharyngeal exudate in pregnant women who addressed to the emergency department and admitted afterwards. According to the procedure at that time, the patients found positive were transferred to the "Pius Brinzeu" Emergency County Clinical Hospital Timisoara (SCJUPBT), where the

medical care of the cases was continued until discharge. Therefore, the present study included both patients transferred from SCMUT to SCJUPBT – Bega Maternity during the period corresponding to the study.

**Descriptive characteristics of the lot of pregnant women.** The group of pregnant women in whom the diagnosis of pregnancy was established and the presence of SARS-Cov2 infection included 149 eligible patients. The following characteristics were followed: the age of the pregnant woman, gestation, parity and method of obtaining the pregnancy (Table 16)

**Results:** In the total group we found that maternal age (years) had an average of 28.2, mean GA was 33.9 weeks, pregnancies obtained naturally vs. IVF (1.4%). Out of the total group of 149 pregnant women confirmed with SARS-CoV2 infection who presented themselves in an emergency in our hospital, 2 patients with spontaneous abortion were excluded. Possible effects of SARS-CoV2 infection were highlighted in 7 patients (4.76%) in whom pregnancy was completed by abortion in the second trimester of pregnancy. We have identified a number of 19 patients (12.92%) who were hospitalized with the diagnosis of evolving pregnancy and in whom the pregnancy was not completed during that hospital stay. These pregnant women benefited from specific treatments, individualized according to the anamnesis, the results of the clinical and paraclinical examination. Unfortunately, in one of the cases, the evolution was rapidly progressive, the patient dying shortly after being emergently transferred. Pregnancies ended with delivery were 123. Maternal death was recorded in a 36-year-old patient with a 25-week pregnancy at the time of admission to the COVID support hospital. Newborns were tested for SARS-CoV-2, by collecting a pharyngeal exudate immediately after birth. In the group included in the study, no positive test was detected at birth. Most patients (111 out of the total of 123 pregnancies) gave birth at or near term (90,24%). Premature birth under 32 weeks of gestation was present in 12 cases (9.7%). The evolution of these preterm infants was favorable in all cases. This group of preterm infants also included a twin pregnancy that ended at 26 weeks of gestation with unfavorable evolution due to association of maternal pathology, multiple pregnancy, extreme prematurity and IUGR. Of the remaining 11 preterm infants, 3 were IUGR preterm infants,(2.72%) with GA under 32 weeks. All 12 cases of preterm infants were transferred as indicated at the time to the Bega Maternity - "Pius Brinzeu" Emergency County Clinical Hospital Timisoara (SCJUPBT),



## CONCLUSIONS

1. IUGR associated with prematurity below 32 weeks of gestation remains challenging for neonatologists and obstetricians.
2. IUGR associated with extreme prematurity remains a critical health problem in developing countries around the world, being one of the "great obstetric syndromes" associated with placental defects but also one of the significant issues in neonatology mainly due to the associated morbidity, mortality and with an significant economic impact.
3. During the 6 years between 2016-2022, the incidence of prematurity under 32 weeks GA in our maternity ward was 3.74%, and of the IUGR premature infants was 2.41% out of a total of 16485 newborns during this period. In the 6 years there were a total of 618 preterm infants with VG under 32 weeks and of these, 59 died, representing a percentage of 9.54%.
4. The need for stricter diagnostic criteria still remains a problem (out of the 220 pregnancies diagnosed with prematurity and IUGR, Doppler measurements were performed on 145 pregnancies)
5. Doppler ultrasound is the most accurate and non-invasive method of assessing placental and fetal function as well as pre- and postnatal diagnosis.
6. Management of a fetus with IUGR and prematurity should include a balance between the risks of chronic intrauterine hypoxia with delivery before term and its associated risks.
7. The incidence of prematurity with IUGR was more common in pregnant women aged 18-30. The majority of pregnancies, respectively 516 (83.5%) of 618 were singleton pregnancies, obtained naturally 597 (96.6%), and a small percentage of the total premature pregnancies (618) were obtained through IVF (21, 3.4%), and the method of birth was more frequent a caesarean section (403, 65.2% vs. natural birth 215, 34.8%)
8. A percentage of 95.19% of all premature pregnancies were complicated (HTAIS, gestational diabetes, chorioamnionitis, placental insufficiency, PRM over 18 hours, multiple pregnancies), chorioamnionitis being in a percentage of 19.64%, much lower than the literature, the probable cause being the incorrect diagnosis of chorioamnionitis (lack of histological diagnosis of histological) but statistically

significant ( $p < 0,001$ ) for premature pregnancies with IUGR remains HTAIS, preeclampsia/eclampsia, placental insufficiency, GDM)

9. We identified through study 1 and 6 the maternal risk factors involved in the prematurity of the IUGR and found that the administration of antenatal corticotherapy in the case of women with imminent risk of premature birth in the total group was administered in a percentage of 70.2%. Antenatal corticotherapy has benefits in reducing the severity of RDS and it is recommended to be administered to all pregnancies at risk of premature birth, including in pregnancies with GDM, chorioamnionitis, PRM over 18 hours but damage to placental and fetal angiogenesis still remains a controversial topic .
10. The maternal causes most commonly involved in prematurity associated with IUGR in our study were GDM, preeclampsia-eclampsia, HTAIS, PRM over 18 hours, and young age. Nutrition, the pandemic period with SARS-COV2 (2 years) with the involvement of behavioral factors, which meant an insufficient pregnancy follow-up, daily stress, smoking, the pathological chain PGDM – thrombophilia – thyroid pathology, have considerably influenced the evolution of pregnancies at young ages.
11. A correct diagnosis of IUGR prematurity involves a correct obstetrical diagnosis, Doppler measurements, as well as a correct neonatal diagnosis.
12. Collaboration with obstetricians, although hard at the onset of study 2 could be achieved in a number of 152 premature newborns with VG under 32 weeks and IUGR, extremely useful to calculate the hypoxia index – Arbeille – HI over 3 or 5 days maximum (although studies show that the determination of this index is made over a period of 15 days), and as HI increases above 100 in our study to values of  $HI \geq 85$  we decided to extract the fetus and decrease the CPR below 1.1 we considered it absolutely necessary to urgently extract the fetus.
13. With the onset of the phenomenon of centralization of circulation (the end-diastolic flow of the umbilical artery absent or reversed) we found that preterm infants with IUGR without centralization of circulation ( $HI \leq 85$ ,  $CPR > 1$ , RI over 0.65) had significantly fewer complications (IVH, LPV, paralytic ileus) compared to the RCIU preterm infants who presented the centralization of circulation.
14. I considered as a considerable contribution, thinking the only one in our country the calculation of this hypoxia index (HI) this represents a precursor of the extraction of a premature fetus with RCIU, with the appearance of the phenomenon of centralization of circulation. The correlation of HI with the values obtained by intrauterine Doppler

allowed us to find that in our study the period from the onset of the phenomenon of centralization of circulation with the decrease in CPR and the increase in  $HI \geq 85$  is 3-5 days and that it involves important cerebral and splanchnic complications. I believe that it is necessary to continue the study in several level III maternity wards in the country, in order to establish an optimal HI value at which the premature newborn RCIU can be delivered, which in my opinion could considerably improve the prevention of hypoxic brain damage, which are one of the most common causes of morbidity and perinatal mortality.

15. We found that preterm infants with GA under 32 weeks and IUGR in which the phenomenon of centralization of circulation was installed, have an Apgar score below 7 to 1 minute and 5 minutes and require resuscitation at the delivery room either with a T-piece resuscitator or the PPV on bag and mask, but also prolonged resuscitation with PPV, ECM, endotracheal intubation, which is correlated with their exposure to chronic intrauterine hypoxia and the subsequent risk for early and medium-term neonatal complications.
16. We monitored for 4 - 5 hours after birth, real-time, somatic and cerebral oxygenation through NIRS that we correlated with Doppler indices by cranial ultrasound through the anterior fontanelle, in coronal and parasagittal section at 24, 48 hours and 3 days. The decrease in RI on ACA secondary to the phenomenon of centralization of circulation, in the first 24 hours postnatally by the loss of the phenomenon of self-regulation associated with the NIRS monitoring initiated in the first 24 hours, allowed me to notice the following: IUGR preterm infants without circulation centralization, with cerebral  $rsO_2 > 50$  had significantly fewer complications (IVH, PVL) compared to the IUGR preterm with the centralization of circulation and cerebral  $rsO_2 \leq 50$  in which cerebral and splanchnic complications were important. This was extremely useful to me in managing respiratory and drug therapy, namely oxygen therapy and the use of positive inotropic medication. The premature infant with IUGR is an extremely vulnerable category in terms of hyperoxia, which causes inhibition of vascular development, accumulation of free radicals, the installation of apoptosis, deficiencies in IGF1-type growth factors in the brain, lung and eye. By using NIRS we have minimized the fluctuations of the cerebral perfusion simply by monitoring these newborns, finding that an increase in cerebral  $rSO_2$  precedes a severe IVH and a sustained decrease in cerebral  $rsO_2$  can contribute to the appearance of lesions of the white matter substance. Although further research is needed to elucidate true prognostic value, cerebral hemodynamic trends measured in cerebral  $rSO_2$  can potentially help detect regional perfusion changes that contribute to IVH

pathophysiology. Extremely useful in managing treatment with positive inotropic agents (e.g. Dopamine) in secondary systemic hypotension, respectively the timing of dopamine administration as the slow and deficient cerebrovascular adaptation occurs. Splanchnic monitoring contributed to the initiation of enteral nutrition, a rather risky stage in this category -by the appearance of paralytic ileus and the risk of spontaneous perforation secondary to the deprivation of the intestine of oxygen, or NEC. I believe that by monitoring NIRS and RI on the cerebral arteries we have helped to avoid possible catastrophic complications arising against the background of a multiorgan chronic hypoxia that can represent an algorithm for the treatment of complications occurring in this category. The lower the GA, respectively, the group 24-26, 26-28 weeks, the more severe the cerebral and splanchnic complications were. Primary NIRS monitoring can detect periods of lower brain oxygenation and altered brain self-regulation, identifying preterm infants at risk of mortality or severe brain damage.

17. The complex monitoring carried out immediately after birth – cerebral ultrasound, NIRS – allowed us to understand that changes in cerebral and splanchnic hemodynamics may persist after birth, which implies a different attitude regarding the monitoring and clinical management of the brain and mesentery of the preterm newborn with IUGR compared to the preterm without IUGR – which is why the cerebral and splanchnic monitoring of real-time oxygenation allowed us a different approach in the interpretation of cerebral and mesenteric oxygenation and the correct use of the therapeutic protocol. An improved understanding of the relationship between altered hemodynamics and brain and somatic oxygenation can inform future strategies to prevent brain and splanchnic injuries.
18. RDS in the premature newborn with IUGR and centralization of circulation, had a weak response to the administration of exogenous surfactant, knowing that in this category of newborns on the production and function of endogenous surfactant primarily acts hypoxia and due to the IUGR the inhibition of surfactant function occurs to which is added a degree of PPHN by excessive pulmonary vasoconstriction secondary to chronic intrauterine hypoxia, sometimes aggravated by acidosis.
19. Related to the SARS-Cov2 pandemic in 2020 during the study period, a number of 147 pregnant women positive for SARS-Cov2 were registered in our maternity ward, reported to 3652 births, but we did not identify any positive newborns through SARS-Cov-2 RT-PCR testing. SARS-CoV2 infection can be a cause of premature onset of labor and the percentage of premature newborn with IUGR was 2.72%. In the studied group (147 pregnancies), premature birth was present only in 9.7% of patients. In all

these cases the development was favorable for newborns. Fetal transmission remains a controversial topic, requiring further data and the establishment of clear diagnostic criteria in order to be able to say with scientific certainty whether or not there is a possibility that SARS-CoV-2 is transmitted to the fetus. The association of SARS-CoV2 infection with extreme prematurity and IUGR continues to remain a concern.

20. The low birth rate in recent years in Romania as well as the increase in the prematurity rate from 8% to 12% made me understand the need for our involvement as neonatologists, obstetricians and psychologists in:
  - Information campaigns on prematurity as a current health problem
  - Elaboration of brochures with the starting point of the family doctor, including the monitoring of pregnancy and the importance of dispensing pregnancy and the risk as well as the causes of prematurity.
  - Prenatal counseling programs for all pregnant women at risk of premature birth, in order to understand and prepare for this moment.
21. The delivery of a premature infant with IUGR and GA under 32 weeks continues to concern obstetricians and neonatologists alike around the world, the optimal time still continues to remain a challenge to avoid the occurrence of complex early and late complications. This is why through this study I propose a combined algorithm of antenatal diagnosis (CPR and HI) and postnatal (IUGR type, type of prematurity, association of prematurity with IUGR, correct assessment of GA, cranial ultrasound, NIRS, early and medium-term complications and their correct treatment)
22. The delivery of a premature infant with IUGR with GA under 32 weeks remains a problem of the obstetrician-neonatologist collaboration, because the IUGR is most often early and the birth occurs at lower GA, with the involvement of the risks of extreme prematurity associated with the morbidities of the RCIU.