"GRIGORE T. POPA" UNIVERSITY OF MEDICINE AND
PHARMACY OF IASI

SUMMARY OF PhD THESIS

ASSESSMENT AND MANAGEMENT OF INTRAUTERINE GROWTH RESTRICTION

Supervisor,

Prof. SOCOLOV Demetra Gabriela, PhD

PhD candidate,

SOLOMIȚCHI (married VIȘAN) Valeria

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In this summary I have included a selected bibliography and iconography, but the content and numbering in the thesis are preserved.
Keywords: fetal growth, intrauterine growth restriction, fetal wellbeing, chronic fetal distress, predictive serum markers, PAPP-A1, mean platelet volume, sFlt/PlGF, uterine artery Doppler, umbilical artery Doppler, cerebral Doppler, fetal MRI, placenta in intrauterine growth restriction.

Abbreviations (selected)

AGA	appropriate-for-gestational-age
ACM - PI	middle cerebral artery-pulsatility index
ACM	middle cerebral artery
OH	obstetric history
ASPRE	combined Multimarker Screening and Randomized Patient treatment with Aspirin for Evidence-Based Preeclampsia Prevention
STCS	segmental transverse cesarea section
DV-PI	ductus venosus-pulsatility index
EFW	estimated fetal weight
CPI	cerebroplacentar index
CCL	craniocaudal length
IUFD	intrauterine fetal death
MPV	mean platelet volume
PAPP-A1	pregnancy-associated plasma protein – A1
PlGF	placental growth factor
PE	preeclampsia
FLM	the first day of the last menstruation
FBP	Fetal biofizical profile
PROGNOSIS	Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia Study
IUGR	intrauterine growth restriction
MRI	magnetic resonance imaging
SGA	small for gestational age
WG	weeks gestation
sFlt-1	soluble fms-like tyrosine kinase-1
s-Eng	soluble endoglin
MBP	mean blood pressure
UA-PI	umbilical artery pulsatility index
UtA-PI	uterine artery pulsatility index
VEGF	vascular endothelial growth factor

1. Introduction

Fetal wellbeing is the sum of all the appropriate conditions offered to the fetus for harmonious intrauterine development. Harmonious development and fetal growth are complex processes that are genetically determined and dependent on the maternal-fetal relationship. Maternal-fetal communication includes a complex exchange of metabolites, hormones, growth factors between mother and fetus, which can be negatively influenced by environmental factors, associated or preexisting maternal medical conditions, but also by fetal and ancillary factors - the fetal ecosystem (1).

Fetal growth potential can be impaired when one or more factors that make up this *intrauterine fetal ecosystem* are impaired.

2. Current knowledge

Early determination of fetal wellbeing alteration and especially of some markers for the early prediction of intrauterine growth retardation (IUGR) and also markers for predicting late-onset IUGR of vascular causes are current challenges for modern obstetrics.

Another challenge is represented by the management of pregnant women at risk for IUGR, so that pregnancy monitoring to be appropriate to these cases, and delivery to take place at the optimal time, both in terms of intrauterine conditions and gestational age. Iatrogenic premature delivery will increase peri- and neonatal morbidity and mortality.

Prolonged exposure of the fetus to the hostile intrauterine environment hampers fetal development leading to IUGR with a negative impact on the cardiovascular (2), neurological (3), renal (4), and metabolic (5) development of the newborn and later of the adult.

Placental insufficiency due to inadequate trophoblastic invasion is responsible for the occurrence of the following conditions during pregnancy: preeclampsia (PE), eclampsia (E), uteroplacental apoplexy (UPA), IUGR, intrauterine fetal death (IUFD).

Poor vascular remodeling occurs as a result of altered balance between proangiogenic factors (fibroblast growth factor, VEGF- vascular endothelial growth factor, PlGF - placental growth factor) and antiangiogenic factors (soluble endoglin, tyrosine kinase 1 - sFlt-1), which will consequently cause a degree of placental insufficiency with repercussions on fetal growth (6,7). The proteins with antiangiogenic role act via different mechanisms which at some point in time may combine causing severe endothelial damage with severe PE (8,9).

Zeisler et al. have demonstrated that a sFlt/PlGF ratio less than or equal to 38 can be used as a marker in predicting the occurrence in one week of PE, E, and HELLP with a negative predictive value of 99.3% (95% confidence interval [CI] 97.9% to 99.9% (10).

The ASPRE trial showed that in the singleton pregnancies in which factors of increased risk for preterm PE were identified by combined first-trimester screening (determination of mean blood pressure (MBP), PAPP-A1 (pregnancy-associated plasma protein - A1), PlGF, UtA-IP (uterine artery pulsatility index), daily administration of aspirin 150 mg in the evening, from 11-14 until 36 weeks' gestation reduces the incidence of preterm PE by 62% (11–14).

Distinguishing between a healthy but constitutionally small fetus and a fetus affected by IUGR is another challenge of modern obstetrics. Doppler ultrasound is the primary tool for distinguishing these fetuses (15–18). Histopathologically, IUGR is the expression of a complex placental disease.

The most common placental lesions are extensive areas of placental infarction, intervillous thrombosis, subchorionic thrombosis, excessive fibrin deposition, and chorionic deficiency by development (19,20). Fetal thrombotic vasculopathy can be the cause of neonatal cerebral palsy or other forms of fetal neurological impairment and is all the more severe as acute hypoxia lesions overlap during labor. Fifty-two percent to 65% of full-term newborn infants present

with dysfunctional insufficiency phenomena immediately postpartum or during the first years of life. In cases with severe perinatal asphyxia, it is important to know the pre-existing placental lesions, as these cases can become forensic cases (21,22).

3. Results generated by the doctoral research

3.1 *Retrospective case-control study conducted at the Necker-Enfants-Malades Maternity Hospital in Paris, which highlights the risk factors for IUGR.*

The ***objectives*** of this study were:

• to identify predictive factors of SGA (small for gestational age) and IUGR fetuses by selecting pregnant women at risk by:
- a thorough clinical assessment of the pregnant woman;
- physical examination: MBP, body mass index (BMI);
- early determination of serum markers at 11-13 weeks gestation;
- Doppler assessment of blood flow in the uterine arteries.

• to determine the role of prophylactic aspirin in pregnant women at risk of PE or SGA.

The study aimed to to develop a screening protocol for pregnant women at risk, as the detection, follow-up, and especially the management of these cases is essential for a good fetal and neonatal prognosis.

Material and methods

To achieve the proposed objectives, I conducted a retrospective case-control study at the Necker-Enfants-Malades Maternity Hospital in Paris, the Reference Center for Ultrasound Detection and Prenatal Diagnosis. This study was made possible by the scholarship won in the project developed at the Iasi "Gr. T. Popa" University of Medicine and Pharmacy: Program of excellence in multidisciplinary doctoral and postdoctoral research in chronic diseases, contract identification number: POSDRU/159/1.5/S/133377.

The data of 5546 women with singleton pregnancy who delivered after 24 weeks of amenorrhea were collected from the ASTRAIA database and studied. The cases were divided into two study groups, according to birth weight:

Group I - **549** pregnant women who delivered infants with birth weight below the 10th percentile (<2670 g), considered the study group. This group was subsequently subclassified according to UtA-PI measured by first-trimester ultrasound:

• SGA fetuses with UtA – PI> 95th percentile = 67 cases;

• SGA fetuses with UtA-PI <95th percentile = 482 cases.

According to the literature data, the UtA-PI> 95th percentile, which corresponds to an average UtA-PI value of 2.35 when determined transabdominally at 12 weeks was considered pathological (23,24).

Group II - **4997** pregnant women who gave birth to infants with birth weight between the 10th percentile and the 90th percentile, considered the control group.

Results

In the first stage of this study we identified possible predictive markers for IUGR as a result of birth weight classification. Thus, we found significant differences between the two groups (SGA vs AGA -appropriate for gestational age) in: **BMI** - 23.74 ± 5.99 kg/m2 vs 22.32 ± 4.00 kg/m2, p = 0.00, **smoking status** - 24.3 vs 19.9%, p = 0.016, **MBP** showed statistically significant differences: 82.82 ± 7.83 in group I, vs 81.62 ± 8.16 in the control group, p = 0.012 and history of IUGR pregnancy - 2.6% vs 1.25%; p = 0.018.

In the two groups, the race showed statistically significant percentage differences. Thus, the European race predominated in both study groups (75.8% vs. 82.7%); however, a higher frequency of African race in the group of newborn infants with birth weight below the 10th percentile, compared to the control group (15.8% vs 9.1%) (p = 0.001) deserves mention (fig.VII.16).

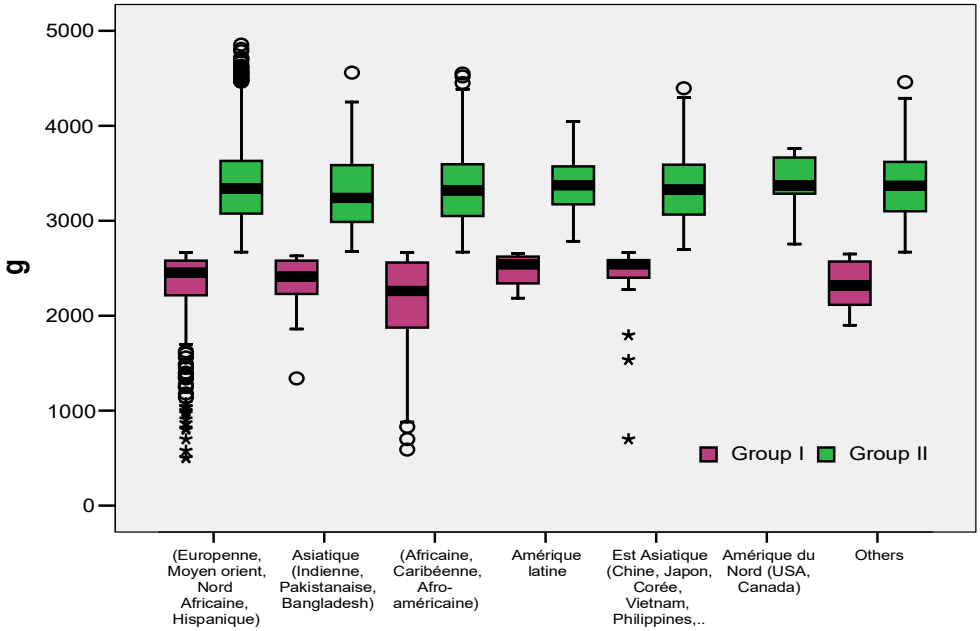

Fig.VII.16. Comparative race-dependent mean birth weight in the two groups

Serum markers studied in the first trimester of pregnancy which showed significant variations were: in group I, mean **PAPP-A1** level was 1.04 ± 0.68 MoM, in 17.1% of cases PAPP -A1 level being below 0.5 MoM, while in group II mean PAPP-A1 level was 1.19 ± 1.20 MoM and only 8.4% of the cases with PAPP-A1 level below the threshold of 0.5 MoM; p = 0.014); mean platelet volume (MPV): in group I, MPV ranged from 8,40 fL to 13,90 fL compared to batch II where it ranged from 10,10 fL to 11,60 fL, statistically insignificant, p = 0.704. In 7.7% of group I cases, MPV was over 10 fL, while in group II, only 2.9% of the determinations exceeded the threshold of 10 fL, p = 0.001.

Since by plotting the ROC curve for the fetal markers monitored in the first trimester of pregnancy we could not identify a good predictor of low birth weight we subclassified the SGA group into UtA-PI according to 2 subgroups (known being the fact that Doppler changes in Uterine arteries occur as a result of poor placental development/inadequate placental development:

- subgroup with UtA-PI over the 95th percentile
- subgroup with UtA-PI below the 95th percentile

No significant differences were found between the SGA group with UtA> 95th percentile and the SGA group with UtA <95th percentile and AGA group in terms of the following variables: age of pregnant women, diabetes mellitus, autoimmune diseases, digestive diseases, gynecological diseases, lung diseases, liver diseases, conception and also obstetric history (PIH -pregnancy-induced hypertension, PE, E, HELLP, IUGR), but statistically significant variations were identified between the SGA group with UtA> 95th percentile vs control group (BMI : p =

0.001, chronic hypertension: p = 0.020, African race = 0.001, MBP p = 0.027, and smoking status p = 0.049).

Mean PAPP-A1 level in the SGA group with UtA-PI> 95th percentile showed statistically significant differences compared to the SGA group with UtA-PI <95th percentile: 0.87 ± 0.48 MoM vs 1.06 ± 0 .70 MoM, p = 0.029. MPV> 10 fl was identified in 11.9% of cases in the SGA group with UtA-PI> 95th percentile and in 7.1% of cases in the SGA group with UtA-PI <95th percentile, statistically insignificant percentage differences, p = 0.244, but significant compared to AGA group, p = 0.001. Mean βHCG value showed no statistically significant differences between study groups (p = 0.727).

Thirty-five point eight percent of women with pathological Doppler gave birth by cesarean section vs. 28% in the group with normal UtA-PI vs. 24.5% in the AGA group.

Of the 5546 pregnant women, only 50 who had at least one risk factor for PE according to the ASPRE study (12,14) received prophylactic treatment with Aspenter.

Discussions

UGR has multifactorial etiology and is incompletely elucidated. Ultrasound diagnosis of a SGA fetus is a late stage in the diagnosis of this condition, so the importance of determining some early risk factors for IUGR is an important goal of modern obstetrics.

One of the main roles of the screening of pregnant women diagnosed with SGA fetus is to detect following a thorough etiological assessment the possible risk factors, (25), which ideally should be included in the primary screening of pregnant women since the first consultation prenatal.

Screening for the risk of IUGR since the first trimester of pregnancy involves the initiation of secondary prophylaxis with Aspenter (ASPRE study) (12,14) and the adaptation of the appropriate medical attitude, so that neonatal morbidity and mortality to be greatly reduced.

Through this retrospective study the following were analyzed: the influence of external and internal factors (i.e. pregnancy-associated or pregnancy-induced diseases) on fetal growth, but also their subsequent monitoring and management. Thus, the studied factors involved in IGS were: BMI (26–28), gynecological diseases (29), pregnancy-associated medical conditions, race (30) smoking status, cardiovascular diseases, obstetric antecedents (OA): parity, history of IUGR, complications of hypertension (PE, E, HELLP, UPA) (25.30).

In our study, **BMI** was a statistically significant variable, both in the SGA group: 23.74 ± 5.99 kg/m2 and in the AGA group 22.32 ± 4.00 kg/m2, p = 0.001. In agreement with the literature data, in our study obesity was associated with IUGR. Thus, in the presence of a reduced nutritional intake in obese pregnant women (31) or of chronic vascular and/or metabolic diseases (metabolic syndrome X) (32), diabetes mellitus (28), pre-existing hypertension (27), fetal growth is affected, and perinatal morbidity and mortality is due to the additional complications (33). The pathogenesis of IUGR in these cases is related to a deficient placentation due to chronic vascular pathology.

Race. Of all my PhD studies, this is the only one that includes a multiracial population. The other studies deal only with the Romanian population, almost 100% Caucasian. Thus, this study showed that the African race is at a higher risk of SGA than the Caucasian race (30), even if the European race predominates. A higher frequency of newborns with birth weight below the 10th percentile (15.8% vs 9.1%) (p = 0.001) was demonstrated in group I patients of the African race compared to group II (fig.VII.16).

Smoking status proved to be a statistically significant variable in our study, namely: 24.3% in group I vs 19.9% in group II, p = 0.016. The estimated relative risk of SGA was 1.26 times higher in group I than in group II. Smoking is considered the major risk factor for SGA, which can be prevented. Both nicotine and the other products that result from burning tobacco influence fetal growth. The mechanism of action of these products is not fully known, but there

are studies that have shown that in cases of smoking cessation from the onset of pregnancy the risk of SGA is greatly reduced (34).

Chronic hypertension is, according to the literature, a major risk factor for IGS (25.30). Thus, in our study were identified significant percentage differences of pregnant women with chronic hypertension in the SGA compared to the AGA group: 1.5% vs 0.7%, p = 0.064.

MBP associated with serum and biophysical markers was also found in our study as in the literature to be predictive markers for PE and SGA (35,36). MBP has been used in numerous studies as a clinical marker for predicting PE and/or SGA in combination with biochemical markers (PAPP-A1, PlGF) and Doppler markers (UtA-PI) (36,37).

Indicators of placental dysfunction for PE and SGA.

A modern approach is based on the principle of integrated screening, based on the model of integrated aneuploidy screening proposed by Nicolaides. It was found that screening t that associates maternal risk factors resulting from case history (medical history, obstetric history, (AOP), UtA-PI, MBP, and biochemical markers: PAPP-A1, PlGF) can identify approximately 90% of women. who will develop early PE at or before 32 weeks gestation, 75% of those who will develop late PE at or before 37 weeks gestation, and 45% of pregnant women who will develop late PE after 37 weeks gestation, with a false positive rate (RPF) of 10% (13.35–37). The ASPRE study showed that pregnant women identified to be at risk for early PE by combined screening and who benefited from the prophylactic administration of Aspirin (150 mg/day, from 11-14 to 36 weeks gestation) showed a reduction. in the incidence of early PE of 89% compared with the placebo group, but had no effect on the incidence of late PE (14). Aspirin-related decrease in IUGR incidence was mainly due to its low incidence as a result of decreased incidence of PE pregnancies. Thus, for IUGR, the incidence was approximately 70% in infants born at less than 37 weeks gestation and 90% in those born before 32 weeks gestation. Thus, it was estimated that first-trimester screening for early PE detection and aspirin administration in the high-risk group could reduce the incidence of late and early IUGR by 20% and 40%, respectively (38). It has been shown that low plasma PAPP-A1 levels in the I trimester of pregnancy are associated with a higher risk of IUGR, (39,40). PAPP-A1 level values <0.5 MoM indirectly indicate disruption of the placental process, i.e. a placental insufficiency with repercussions on fetal growth (41).

In our study we analyzed the relationship between **PAPP-A1 and SGA**. Thus PAPP-A1 levels ranged from 0.07 to 6 MoM, in 17.1% of pregnant women with SGA (group I) below 0.5 MoM, while in group II, pregnant women with AGA fetuses, PAPP-A1 values ranged from 0.08-93 MoM, with only 8.4% below the 0.5 MoM threshold. Thus, mean PAPP-A1 level was significantly lower in group I compared to group II (1.04 ± 0.68 vs 1.19 ± 1.20 MoM; p = 0.014).

Another studied possible marker for IUGR prediction was **mean platelet volume** (MPV). MPV reflects platelet activation due to inadequate placentation. Kanat-Pektas et al. in 2014 showed that there is an association between high MPV values and low birth weight (42).

Even though according to the literature there is an association of low birth weight with MPV values above 10 fL, the average value of MPV in our study did not correlate significantly with birth weight (r = - 0.004; p = 0.998) although the number of pregnant women with MPV above 10fL was significantly higher in the SGA group compared with AGA group, namely 7.7% vs 2.9% (p = 0.001).

Because from a pathophysiological point of view deficient placentation is the underlying cause for the development of various diseases during pregnancy, we tried in our study to establish whether there is a correlation between PAPP-A1 and first-trimester **uterine artery Doppler changes**.

Khalil et al. concluded based on their studies that PAPP-A1 and UtA-PI, determined at 11-13 weeks gestation can be used as markers for the early detection of cases at risk of IUGR.

Thus, in the group of pregnant women with SGA without PE compared to the control group, UtA-PI showed high values (1.10 vs. 1.00 MoM), but PAPP-A1 had low values (0.85 vs. 1.00 MoM).

In the group of pregnant women with SGA and PE UtA-PI levels were also high (1.40 vs. 1.00) and PAPP-A1 levels low (0.72 vs. 1.00 MoM). This study reflects a manifest placentation deficiency at 11-13 weeks gestation by reduced PAPP-A1 and increased UtA-PI, which in the long term may lead to PE and/or IUGR (43).

Changes in Doppler parameters were also recorded in this study; using Doppler criteria the SGA group was subclassified as follows:

- SGA subgroup with UtA-PI> 95th percentile 95 = 67 cases with defective placentation that can be detected starting with the first trimester of pregnancy and require prophylactic treatment with Aspenter according to the ASPRE study (14);
- SGA subgroup with UtA -PI <95th percentile = 482 cases which will be monitored according to the protocol for monitoring risk-free pregnancies.

Statistically, significant differences between these two subgroups and the AGA group were found for the following parameters: BMI p = 0.001; African American race - p = 0.001; smoking status - p = 0.049, MBP - p = 0.0020; chronic hypertension - p = 0.027.

Mean PAPP-A1 level was significantly lower in the SGA group with UtA-PI> 95th percentile (0.87 ± 0.48 MoM) compared to the SGA group with UtA-PI <95th percentile (1.06 ± 0.70 MoM) and the AGA group (1.19 ± 1.20 MoM), p = 0.029, but statistically insignificant between the SGA group with UtA-PI <95th percentile and group AGA: p = 0.179. This finding supports the data in the literature according to which PAPP-A1 can be used as a screening marker together with biophysical markers in the selection of cases at risk of IUGR (41,44–46). MPV> 10fL was identified in 11.9% of cases in the SGA group with UtA-PI> 95th percentile vs 2.9% in the GMS group, p = 0.001, and statistically insignificant among the SGA groups with UtA-PI <95th percentile, in 7.1% cases vs. GMS in 2.9% of cases, p = 0.244.

Differentiation of low weight fetuses by UtA Doppler PI represented a critical point in the revision of IUGR definition and ultrasound diagnosis of this pathology.
The use of Delphi criteria in the classification of SGA fetuses is important, as it separates cases with IUGR at increased risk of perinatal morbidity and mortality and thus requiring adequate monitoring and management from SGA cases in which fetuses are constitutionally small but have a good perinatal prognosis (47).

Included in this study were pregnant women who received prophylactic Aspenter treatment using the FMF criteria (except for PlGF which was not measured), and we studied the frequency of complications during pregnancy in patients receiving and not receiving Aspenter treatment. Thus, in the group of pregnant women on prophylactic Aspenter treatment we identified the following risk factors (UtA-PI, MBP, PAPP-A1, chronic hypertension, history of PE, history of IUGR, autoimmune diseases, BMI over 30kg/m2, age over 40 years) and complications recorded during pregnancy were greatly reduced. The efficacy of Aspenter treatment is thus also confirmed by our study, this being in agreement with the most complex study conducted for this purpose - the ASPRE study (12,14).

We found the following complications in pregnant women who underwent Aspenter treatment compared with those who did not receive this treatment (with pathological Doppler and normal Doppler findings): PIH: 0% vs 0.1% vs 0.1%, PE/E: 2% vs 1.3% vs 1.7%, intrauterine fetal death: 0% vs 0.4% vs 0.4%, SGA: 14% vs 10.9% vs 8.5%, IUGR: 0% vs 1% vs. 0.7%.

The complications recorded in the newborns also showed significant differences, namely: Apgar score less than 7 at 5 minutes: 0% vs 2.1% vs 2.2%, hyperbilirubinemia 4% vs 1.2% vs 0, 48%, p = 0.015, hypoglycemia 6% vs 0.5% vs 0.36%, p = 0.001, hypocalcemia: 4% vs 0.4% vs 0.46%, p = 0.018; more severe complications were detected in newborns with IUGR and

pathological Doppler finding and who did not receive prophylactic Aspenter treatment: necrotizing enterocolitis in 5% of cases, cerebral hemorrhage in 0.7% of cases, and respiratory distress in 1.5% of cases. Thus, in agreement with the data in the literature, we found that the administration of Aspenter 50mg/day after the first-trimester combined screening until 36 weeks gestation reduces the number of PE and SGA cases, also improving the prognosis of the newborn and thus reducing neonatal morbidity and mortality (14,38).

Conclusions

- In this study we identified maternal anamnestic factors associated with a high risk of IUGR: African race, chronic hypertension, obesity, and smoking status;
- Decrease of PAPP-A1 <0.5 MoM indicates a deficient placental function, caused by uteroplacental vascular insufficiency, pathophysiological mechanism with repercussions on fetal growth;
- First-trimester screening, revealing the maternal risk factors, MBP, and determining the biochemical markers (PAPP-A1) and biophysical markers (UtA-PI), is the essential element in predicting pregnancies at risk of PE or and IUGR and in initiating prophylactic treatment with Aspenter to reduce fetal and neonatal morbidity and mortality;

  Perturbation of fetal growth can also be detected in pregnant women without maternal risk factors; thus, pregnant women should be selected based on the presence of risk factors but also by determining first-trimester biochemical and biophysical markers capable of identifying the increased risk of developing IUGR.

3.2. Retrospective case-control study conducted at the Iasi "Cuza Voda" Maternity Hospital aimed at detecting the predictive factors for IUGR based on clinical assessment and first-trimester ultrasound

Objectives and motivation of the study

The objective of this study is to identify pregnant women at risk of IUGR, by identifying the maternal, fetal and placental risk factors, as well as the management of these cases to improve the neonatal prognosis.

The motivation for this study is, as in the previous study, to develop an appropriate screening and management protocol for pregnant women at risk of IUGR. Unlike the previous study, the aim of this study was to detect the possible particularities related to the risk of developing IUGR in Romanian pregnant women as well as those related to IUGR screening in Romania by identifying the maternal, fetal and placental risk factors, as well as the management of these cases to improve the neonatal prognosis**.**

Material and methods

To achieve this goal we conducted a retrospective case-control study that included pregnant women> 24 weeks gestation admitted to the Department of Obstetrics - Gynecology II of the Iasi "Cuza Voda" University Maternity Hospital between 01.01.2013 - 30.06.2015 for fetal wellbeing monitoring and childbirth assistance:

Group I - 54 pregnant women with an estimated fetal weight below the 10th percentile (48.2%), SGA fetuses.

The cases found at third-trimester ultrasound as <10th percentile were subdivided according to Delphi criteria (47) into three subgroups: early detected SGA <32 weeks gestation,

late detected SGA> 32 weeks gestation, and SGA. In the early detected SGA group, applying the Delphi criteria for IUGR 5 cases with early IUGR (<32 weeks gestation) were found.

In the late detected SGA group> 32 weeks gestation, applying the Delphi criteria 27 cases with late IUGR (> 32 SG) were found: According to this classification the study patients belonged to the following groups:

- **Early IUGR**: 5 cases;
- **Late IUGR**: 27 cases;
- **SGA**: 22 cases.

Group II - control group that included 58 pregnant women with fetal weight ranging from the 10th to the 90th percentile (51.8%), AGA fetuses.

Fetal weight was estimated by ultrasound using biometric parameters for weight calculation (DBP, HC, LF, CA). Fetal morphology was evaluated ultrasound at 12 and 22-24 weeks gestation.

Gestational age was calculated from the first day of the last menstrual period and confirmed or dated by determining CRL (crown-rump length) at first-trimester ultrasound.

Results

Of the multitude of assessed maternal risk factors, in group I significant in the causation of early IUGR compared to late IUGR were: malformed uterus (p = 0.001), fibromatous uterus (p = 0.021), history of IUGR (p = 0.011) and obesity (p = 0.035), and compared to SGA, pregnancy-induced hypertension is added (p = 0.048).

The identified Doppler parameters on which the classification according to the Delphi criteria was based are listed in Table VII.18.

Table VII.18. Pathological findings during feral health monitoring

Pathologic Doppler and CTG findings	**Early IUGR (n=5)**		**Late IUGR (n=27)**		**Chi2**	**P**	**OR**	**RR**	**IC95%**
	n	***%***	***n***	***%***					
UA-PI > 95th percentile	2	40.0	10	37.0	0.02	0.902	1.13	1.08	0.33-3.52
UA-ADEV/RDEV	3	60.0	0	0.0	11.51	**0.001**		-	-
ICP < 95th percentile	0	0.0	14	51.9	2,74	**0.098**		-	-
UtA-PI >95 percentile	5	100.0	10	37.0	4.43	**0.035**	2.50	2.70	1.65-4.42
CTG	2	40.0	10	37.0	0.02	0.902	1.13	1.08	0.33-3.52

In the postnatal period, the following were found: of the 32 fetuses diagnosed prenatally with IUGR, 2 newborns were categorized as healthy but low weight (SGA), i.e. they did not present complications and had a favorable postpartum evolution, the remaining 30 newborns presenting the following complications: necrotizing rectocolitis, intraventricular hemorrhage, respiratory distress, hypoglycemia, and hyperbilirubinemia. SGA infants had a favorable postnatal evolution without complications of IUGR.

In group II, of the 58 fetuses diagnosed prenatally as AGA, 10 newborns had lower birth weight, so they were included in the SGA group with favorable postpartum evolution.

The findings of ultrasound imaging of fetal appendages showed that in group I there were no significant percentage differences in the causation of early or late IUGR.

Compared to the AGA group (group II), in the SGA group we found that: decidual hematoma (p = 0.049), placental hypermaturity (p = 0.050,) and oligoamnios (p = 0.014) showed statistically significant differences.

The pathological findings reported during the assessment of fetal wellbeing by Doppler ultrasound and CTG revealed: UA-ADEV was found to be statistically significant only in patients with early IUGR (p = 0.001), ICP below the 5th percentile was significant (p = 0.098) in pregnant women with late IUGR, and UtA-PI over the 95th percentile in pregnant women with early IUGR (p = 0.035).

By plotting the ROC curve, in group I it was found that the 1-minute Apgar score depended on CTG changes with a sensitivity of 60% and a specificity of 60% (AUC = 0.627; 95% CI: 0.353-0.918), (fig. .VII.29).

The estimated risk of UtA-PI above the 95th percentile was 2.70 times higher in patients with early IUGR. There were no significant percentage differences related to early or late IUGR

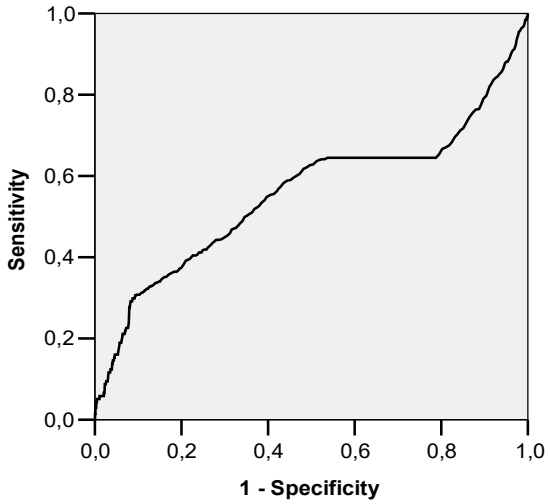

Fig.VII.29. Sensitivity/specificity balance of Apgar score in CTG determinism in the group with fetal weight below the 10th percentile

Discussions

The causes and associated factors that can affect fetal wellbeing and thus fetal growth are numerous and incompletely known. They do not intervene separately, but act through various associations and in various proportions. The presence of risk factors in the absence of abnormal biometry does not justify the patient's desire to seek a second opinion (30,48). Among the demographic factors determined (mother's age, parity, gestation) in this study, we did not notice statistically significant variations.

Of the behavioral factors, smoking status proved to be a statistically significant variable: 25.9% of group I pregnant women and only 5.4% of group II were smokers (p = 0.007), the relative risk of SGA being approximately 4 times higher (RR = 4.84; 95% CI: 1.47-15.9) for pregnant women in group I.

The study by Ong et al. demonstrated that smoking mothers delivered SGA infants (p = 0.0005) compared to infants of non-smoking mothers. These infants were monitored in the first 12 postpartum months, when they were found to have reached the appropriate weight for age (49).

In our study, mean birth weight was significantly lower in infants with late IUGR compared with infants with early IUGR, both born to smoking mothers, namely: 1510g in newborns with late IUGR; p = 0.001 vs 1575g in newborns with early IUGR; p = 0.003.

There is an association between active smoking during pregnancy and SGA frequency with a pronounced effect in people who smoke more than 10 cigarettes a day. Pregnant women should avoid passive smoking exposure starting with the first weeks of pregnancy, as this results in a reduction up to zero of the risk of SGA (25).

Of the pregnancy-related or pregnancy-induced conditions, pregnancy-induced hypertension was significantly more common in group I patients compared to group II (29.6% vs 8.6%; p = 0.004), in which the estimated risk of IUGR was 1.83 times higher, 95% CI: 1.30-2.57. The main complications of hypertension in this study were PE (50%) and HELLP syndrome (37.5%).

The use of Delphi criteria in our study revealed the presence of the following risk factors in group I (SGA group) compared to control group II (AGA group): smoking status (p = 0.007), history of IUGR (p = 0.034), hypertension - IS (p = 0.004), fibromatous uterus (p = 0.032) and malformed uterus (p = 0.046); obesity proved to be a significant risk factor for early IUGR compared to late IUGR (p = 0.035), but also compared to SGA (p = 0.038).

Compared to the study conducted in France, in which maternal factors were not statistically significant variables for the risk of IUGR, except for MBP, smoking status, and obesity, in the study conducted in Romania we found that the statistically significant risk factors for IUGR were: smoking, obesity, PIH, fibromatous uterus, malformed uterus, and a history of IUGR, in agreement with literature data (25.50).

In our study, there were few cases with iron deficiency anemia, gestational diabetes, hereditary thrombophilia, lung disease, CIHS, chronic hepatitis, pregnancy-associated autoimmune thyroiditis, which is why they were not considered statistically relevant risk factors.

In this study changes in UtA Doppler PI were detected in 5 cases with early IUGR and in 10 cases of fetuses with late IUGR, p = 0.035. Thus UtA-PI above the 95th percentile is an important Doppler marker, used in the classification of IUGR fetuses according to Delphi criteria (47), which characterize early IUGR, and its presence will determine a 2.7 times higher risk for the development of early IUGR compared with late IUGR (Table VII.18).

An important study is the one conducted by Herraiz et al who wanted to determine whether high UtA resistance plays a role in explaining low PAPP-A levels in the absence of aneuploidies. They found a significant negative linear correlation between mean UtA-PI and PAPP-A (r = −0.331; P <0.01). After adjusting the PAPP-A values by UtA-PI and the false-positive rate for trisomy 21 decreased from 6.9% to 2.6%. These determinations are very necessary as this way excessive chorionic villi sampling in order to rule out aneuplidy is avoided and imply the administration of Aspirin to pregnant women at risk. As this study was retrospective, we did not find in the medical records all data about the levels of PAPP-A1 and first-trimester MPV to make this correlation

In this retrospective study ***fetal wellbeing*** was monitored by CTG, ICP and ultrasound assessment of fetal appendages.

A reactive CTG reflects an intrauterine environment appropriate for fetal growth, while low variability and decelerations reflect an intrauterine environment hostile to the fetus (52).

A nonreactive CTG with decelerations suggests a poor fetal prognosis, a fact demonstrated by the correlation between CTG and Apgar score. By calculating the ROC curve, we demonstrated that the 1-minute Apgar score depends on CTG changes, having a sensitivity of 60% and a specificity of 60% (Fig. VII.29).

In group I patients, nonreactive CTGs were recorded in 13% of cases and CTGs with deceleration in 5.6% of cases compared to group II, where there were 5.2% cases with nonreactive CTGs and no cases with decelerations, statistically significant findings (p = 0.049). In group I, 40% of patients with early IUGR and 11.1% with late IUGR had nonreactive CTG (Fig. VII.25).

Flynn et al. conducted a study on 301 pregnant women correlating fetal heart rate reactivity with active fetal movements, correlating the reactive or nonreactive CTG tracings with the Apgar score. Thus, they found a statistically significant proportion of cases with Apgar score <6 in the group of fetuses with nonreactive CTG, p <0.001, a fact also demonstrated in our

study, and that the number of cesarean deliveries was high in the group with nonreactive CTG (53).

In our study, early Doppler changes were identified and were at the basis of the decision to deliver. Thus in the group of pregnant women with early IUGR 2 cases with UA-PI over the 95th percentile and 3 cases with umbilical artery reverse flow were identified, reason why emergency cesarean delivery was performed after prophylaxis of hyaline membranes disease with dexamethasone and administration of magnesium sulfate for neuroprotection (Table VII.18).

The Doppler changes occur sequentially in early IUGR cases (<32 SA), followed by a progressive succession of changes due to the persistence of hypoxia. Ferrazzi et al. have classified these changes into: early changes, which were seen in UA and MCA, and late changes, detected by altered blood flow in the ductus venosus and aortic isthmus. Thus, these researchers showed that in 50% of the early IUGE fetuses, early Doppler changes occurred 15-16 days prior to the decision to deliver, while late Doppler changes occurred 4-5 days before the decision to deliver in 50 % of the fetuses with early IUGR. The time interval between the occurrence of early and late changes, and also late changes were significantly associated with perinatal death (P <0.01) (54).

Similar results were found in our study, namely in the group of pregnant women with late IUGR there were 14 cases with PCI below the 5th percentile (p = 0.098), compared to the group of pregnant women with early IUGR fetuses where no changes in ICP were identified (Table VII .18).

Oligoamnios, which occurs due to the phenomenon of centralization of fetal circulation due to hypoxia is one of the statistically significant ultrasound markers (55), was detected while assessing fetal wellbeing in52,9% of group I fetuses compared with 36,2% of group II fetuses (p = 0.014). Not the same was found when comparing the early and late IUGR soubgroups, early IUGR and SGA, and late IUGR and SGA groups.

Ultrasound placental abnormalities (placental insertion pathologies, presence of anechoic areas, first-trimester decidual hematomas, placental abruption, high placental maturity grade for gestational age, ie placental calcifications), were also seen in our studies. The most common of these placental abnormalities detected by first-trimester ultrasound, were found in 81,5% group I cases and 72,4% of group II cases, p = 0,049, and high placental maturity grade in 13% of group I vs 6,9% of group II cases, p = 0,05. The estimated risk for IUGR in these patients was 1.3-fold higher. These placental ultrasound findings suggest deficient placentation starting with the first trimester of pregnancy (decidual hematoma) but also later, in trimesters II - III (increased placental maturity), being more common in the group with late IUGR vs SGA, and especially in pregnant women with oligoamnios.

Chen et al. in a study of placental ultrasound changes found that the presence of premature calcifications before 32 weeks gestation was associated with maternal and neonatal complications: postpartum hemorrhage, PNPNI (premature detachment of a normally inserted placenta), IUGR, IUFD. In contrast to these findings, grade III placenta between 32-36 weeks gestations is not associated with more frequent maternal and neonatal complications than in the control group (56). Thus, early placental changes are a risk factor for adverse perinatal effects, even in the absence of other risk factors. These ultrasound findings can facilitate the identification of pregnant women at risk and their inclusion in a strict prenatal monitoring program.

An IUGR fetus requires continuous intrapartum CTG monitoring if following the assessment of fetal wellbeing and Doppler circulation it was decided that natural birth is possible. The condition of the fetus with IUGR can deteriorate rapidly during labor, as it cannot adapt to the stress resulting from uterine contractions, which is why delivery by emergency cesarean section is indicated (57).

In this study there were both natural and cesarean births: 81.5% of pregnant women in group I and 70.7% of those in group II gave birth by cesarean section, statistically insignificant ($p = 0.180$) because there were also other indications of cesarean delivery.

Compared to the study conducted in France, in the Romanian study we highlighted the increased risk of IUGR in the presence of PIH and the following maternal factors: smoking, obesity, history of IUGR, malformed uterus, and fibromatous uterus. Following the use of the Delphi criteria, we distinguished the SGA cases from prenatal IUGR, and also early IUGR from late IUGR, and we postnatally analyzed the difference in the immediate evolution (until discharge) of IUGR compared to SGA and AGA fetuses/newborns.

By the described correlations I have demonstrated that the monitoring of fetal wellbeing by fetal ultrasound (amniotic index determination, fetal circulation Doppler, fetal heart rate, active fetal movement, placental morphology) and CTGs can improve fetal prognosis through proper management.

Conclusions

1. Explorations to establish the cause of IUGR as well as its diagnosis must follow a rigorous and systematic approach.
2. Fetal prognosis can be improved by determining in the first trimester of pregnancy serum markers, Doppler assessment of the uteroplacental circulation, morphological assessment of the placenta, and initiation of Aspenter prophylaxis.
3. Assessment of fetal wellbeing by Doppler ultrasound of fetal circulation, CTG, and the amount of amniotic fluid has an important role in the management of IUGR pregnancy.
4. From a practical point of view, fetal biometrics is useful for diagnosing a fetus with IUGR or SGA, and Doppler velocimetry and fetal morphology make it possible most often to determine the cause and fetal vital prognosis.
5. The use of Delphi criteria favors the correct identification of cases at risk, and consequently the management will be adequate for each IUGR category, and thus the fetal and neonatal prognosis will be improved.

3.3 Prospective case-control study aimed at identifying possible predictive factors for IUGR.

Objective and motivation of the study

The study **aims** to determine whether PAPP-A1, MPV, MBP levels, placental ultrasound changes, Doppler assessment of uterine arteries, and also a thorough history of the pregnant woman are possible predictors of the risk of IUGR.

The **motivation** of this study is to improve the rate of perinatal morbidity and mortality in pregnant women at risk of IUGR. Current research is focused on determining early predictive serum factors and markers, which will positively influence the prophylactic intervention and follow-up of cases at risk by Aspenter administration 150 mg/day up to 35 weeks gestation as a method of secondary prophylaxis of pregnant women at risk of IUGR.

Material and methods

Prospective study, conducted in the interval August 1, 2014 - September 1, 2015 in 70 pregnant women enrolled in the study at gestational age (GA) 11 weeks 0 days -13 weeks and 6 days. This study consisted of a thorough physical assessment of the pregnant woman, determination of PAPP-A1, MPV, MBP during the screening test for fetal aneuploidies, first-trimester ultrasound assessment of the placenta (presence or not of anechoic or placental abruption areas), and determination of UtA-PI in at least one uterine artery. The pregnant women included in the study presented for outpatient pregnancy monitoring, and the birth took

place in the Department of Obstetrics and Gynecology of the Maternity of Piatra Neamt County Emergency Hospital.

From the characteristics of pregnant women included in the study no statistically significant differences were found between pregnant women at risk of SGA and the controls in terms of: maternal age, BMI, racial origin, diabetes mellitus (DM), as well as mode of conception, gestation, and parity. The criteria for separation were the possible risk factors for SGA or IUGR: smoking status, chronic hypertension, gynecological history, history of pregnancy induced hypertension, PE, E, HELLP, and IUGR in previous pregnancies.

Thus group I pregnant women who had at least one major risk factor or at least two moderate risk factors for PE and/or SGA according to the ASPRE study received prophylactic treatment with Aspenter 150mg/day. Eleven pregnant women did not follow the Aspenter treatment for various reasons (allergies, intolerance). Of these 9 women developed late IUGR of vascular cause and 2 women SGA. In patients who received Aspenter treatment and followed it we recorded 1 case of late IUGR and 29 cases of SGA, and in the control group, while in the pregnant women without risk factors no complications were recorded during the pregnancies.

In pregnant women at risk of SGA, PAPP-A1 level <0.5 MoM was recorded in 73.2% of group I cases and 37.9% of the controls, statistically significant (p = 0.016) (fig.VII.34). First-trimester MPV was >10 fL in 73.2% of group I cases and 27.6% of the controls, statistically significant results (p = 0.001), (fig.VII.35). The estimated fetal weight in the percentiles in group I was 6.1 ± 3.21, significant as compared to the control group 45.6 ± 25.3, p = 0.001.

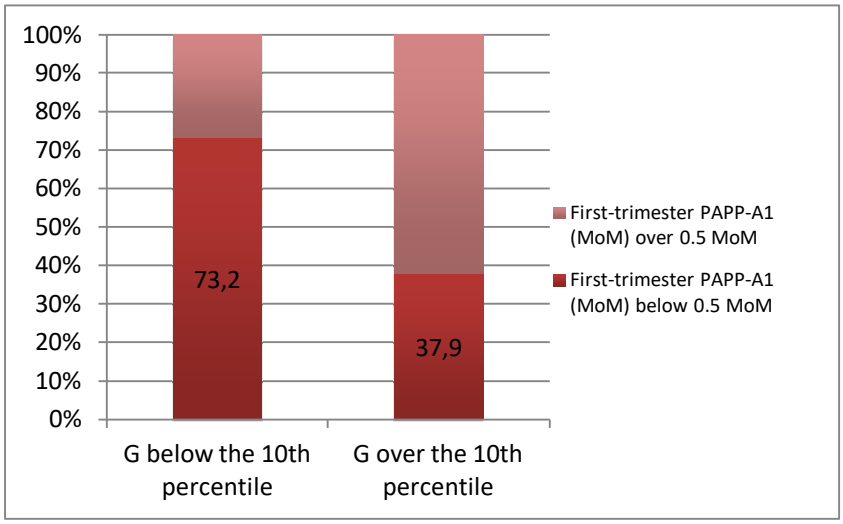

Fig. VII.34. Distribution of cases by weight and PAPP-A1

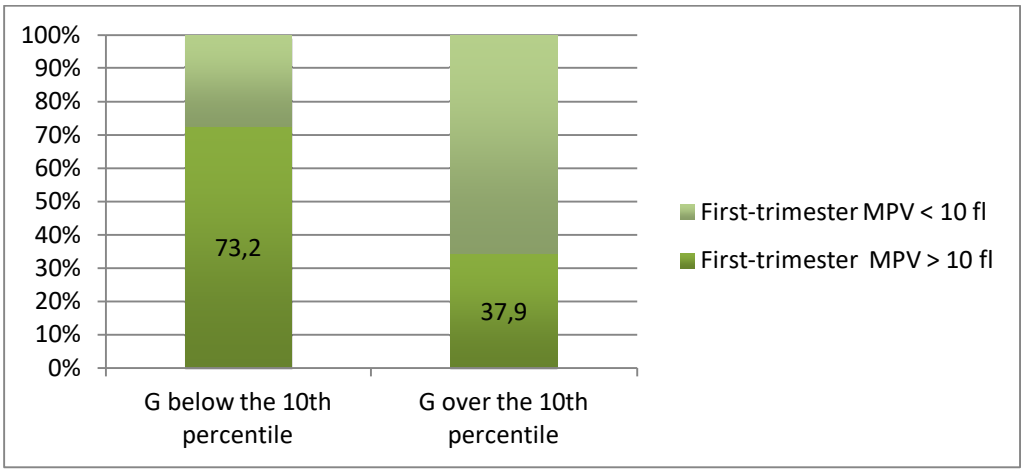

Fig. VII.35. Distribution of cases by weight and MPV

Discussions

It is known that fetuses diagnosed with IUGR have an increased risk of perinatal morbidity and mortality due to complications that may occur. In this context, the determination of some biochemical markers predictive of IUGR found in the maternal circulation after 12-13 weeks gestation is essential.

In our study, of 41 pregnant women with SGA 30 had PAPP-A1 levels <0.5MoM, suggesting a statistically significant correlation between SGA and PAPP-A1 ($p = 0.016$), (fig.VII.34).

Another marker determined in this study was MPV, a predisposing factor of thrombosis demonstrated by the relationship between MPV and SGA. A high MPV reflects platelet activation caused by uteroplacental circulatory failure. In this study we found in 38 pregnant women MPV> 10 fl, and in 30 low birth weight newborns there was a correlation between MPV> 10 fl, and birth weight, $p = 0.001$, (fig.VII.35), findings in agreement with data reported in the literature (42,58,59). A study by M. Kanakt-Pektas shows that the MPV level> 10 fl, can predict IUGR with a sensitivity of 82.4% and a specificity of 60% (42).

In the determined **demographic factors**: mother's age, parity, and gestation we did not identify statistically significant variations. The studied **behavioral factors** were: smoking status, which was a selection criterion for the SGA group being considered a risk factor for IUGR as well as obstetric history (**IUGR in previous pregnancies, PE, E, PIH**), PMH (past medical history) of **chronic hypertension, uterine fibroma** (25,30). The **MBP** determined at the 1st prenatal consultation was higher in the SGA group compared with controls (Table VII.20). This doctoral research but also the studies in the literature demonstrated that the determination of PAPP-A1, MBP, and UtA-PI in the first trimester of pregnancy, and the anamnestic factors may be markers in the screening of pregnant women at risk of IUGR and PE (36.60).

A marker of interest in previous studies is first-trimester UtA-PI measured by ultrasound. In this study UtA-PI and Doppler flow morphology (persistence or not of protodiastolic notch) were determined in all enrolled patients, representative elements for the first wave of trophoblast invasion. Inadequate maternal spiral artery remodeling results in high-resistance uteroplacental circulation, with the occurrence of ischemic placental lesions. Both low PAPP-A1 (46) and high UtA-PI in at least one uterine artery are important data for impaired trophoblast invasion, with long-term negative effects on fetal growth and pregnancy-related diseased: PE, UPA, IUFD (61).

Thirty group I pregnant women followed a treatment with aspirin 150 mg/day, and the occurring complications during pregnancy in these women were: 1 case of late IUGR of vascular cause, remaining patients having SGA pregnancies. No major complications of the prophylactic treatment were recorded. Eleven pregnant women in the group of pregnant women at risk did not follow the recommended treatment with Aspenter for various reasons, and the complications in this group were as follows: 9 cases with late IUGR of vascular causes (7 PIH and 2 PE cases) and SGA in 2 cases.

Due to the Doppler and CTG findings, delivery was by cesarean section. The resulting newborns had an Apgar score at 5 minutes less than 7 and required neonatal intensive care for: respiratory distress (2 cases), hypoglycemia (5 cases), hyperbilirubinemia (4 cases), and necrotizing enterocolitis (1 case).

Placental ultrasound changes (hematomas, anechoic areas) were detected in this study as in the previous study, suggesting deficient placentation with defective development of the villi and implicitly impaired maternofetal exchanges with repercussions on fetal growth (62).

Conclusions

1. The association of first-trimester biochemical markers (PAPP-A1, MPV), MBP, uterine artery Doppler, and placental biophysical parameters, and also of the anamnestic factors are promising elements that can be used in detecting the risk of IUGR;
2. Early detection of pregnant women at risk for IUGR and/or PE requires the initiation of prophylactic treatment with Aspirin 150 mg/day, their careful follow-up during pregnancy, but the optimal timing of delivery thus reducing neonatal morbidity and mortality.

3.4. Prospective case-control study aimed at determining whether the sFlt/PlGF ratio can predict late IUGR of vascular cause in third-trimester pregnant women

The objective of this study was to improve the perinatal prognosis of pregnant women at risk for IUGR by determining the sFlt/PlGF ratio, also known as PE ratio, to increase the quality of monitoring, thus reducing neonatal morbidity and mortality.

The aim of this study was to confirm whether the sFlt/PlGF ratio, also known as the biomarker for PE, reduces the false positive detection rate of late IUGR of vascular causes suspected after an ultrasound scan

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Material and methods.

This is a prospective case-control study conducted in the interval October 1, 2017 - May 1, 2018 at the Iasi "Cuza Voda" Maternity Hospital. This study included a number of 68 cases divided into two groups, depending on the fetal weight estimated by third-trimester ultrasound (28 weeks + 0 days through 34 weeks gestation +/- 6 days):

- Group I - 34 pregnant women with estimated fetal weight below the 10th percentile;
- Group II - 34 control cases, pregnant women with an estimated fetal weight between the 10th and 90th percentiles

The pregnant women included in the study presented to the "Cuza Voda" Maternity for third-trimester ultrasound (28 weeks + 0 days through 34 weeks +6 days).

Results

Table VII.24. Ultrasound data, CTG tracings and levels of biochemical markers at the time of enrolment

Characteristics	**Pregnant women with IUGR, N=37**	**Control group, N=37**	**Statistical tests used**	**P**
First-trimester PAPP-A1 (MoM)	0.71±0.56	0.93±0.50	Student's t-Test	0.23
First-trimester HCG (MoM)	1.66±2.04	1.28±0.75	Student's t-Test	0.48
VG at the time of enrolment	36.7 [32.4-37.2]	34.4 [33.7-36.7]	Mann Whitney test	0.60
VB at the time of enrolment	32.4 [29-34.2]	34.7 [33.6-36.3]	Student's t-Test	<0.001
Fetal weight estimated in percentiles at the time of enrolment	6.4±3.36	46.7±21.58	Student's t- test	<0.001
UtA-PI >1 in at least one UtA	10/37 (66.6%)	5/37 (33.3%)	Fisher test	0.21
Presence of notch in at least one UtA	9/37 (90%)	1/37 (10%)	Fisher test	**0.04**
UA-PI >1	22/37 (73.3%)	8/37 (26.7%)	Chi-square test	**<0.001**
Absent or reversed end-diastolic flow in UtA Absent/negative=pathologic	2/37 (51.6%)	0/37 (48.4%)	Fisher test	0.494
ACM-PI PI< 1.5=pathologic	19/30 (66%)	10/24 (44%)	Chi-square test	0.113
ICP<1	10/37	0/37	Fisher test	0.28
AFI	15/37 (75%)	5/37 (25%)	Fisher test	**<0.001**
CTG at birth				
Abnormal variabilities	7/37	0/37	Fisher test	0.011
Presence of decelerations	4/37	0/37	Fisher test	0.11
Serum markers				
PIGF (ng/mL)	86.6 [42.2-155.35]	459.3 [276.3-1387]	Mann Whitney test	**<0.001**
sFlt-1 (ng/mL)	6394 [3703.5-10187.5]	2402 [1491-3098]	Mann Whitney test	**<0.001**
sFlt-1/PIGF ratio	103.6 [29.2-194.2]	5.20 [1.54-9.34]	Mann Whitney test	**<0.001**

No significant differences were found between cases and controls in terms of: maternal age, maternal BMI, gestational age at the time of enrolment, racial origin (all pregnant women were Caucasian), smoking status, and alcohol consumption, history of chronic hypertension, diabetes mellitus, systemic lupus erythematous, antiphospholipid syndrome, as well as mode of conception (spontaneous or in vitro fertilization), gestation, parity, PIH or PE and its complications: E, HELLP syndrome, and UPA.

The CTG data that included abnormal variability and presence of decelerations; levels of first-trimester biochemical markers (PAPP-A1 (MoM) and β HCG (MoM) (when available), and of the angiogenic markers: sFlt-1, PlGF and sFlt-1/PlGFratio are shown in Table VII. 24.

Mean PlGF level of pregnant women with IUGR was significantly lower than that of the controls (86.6 and 459.3, respectively, p <0.001). Mean sFlt-1 in pregnancies complicated by IUGR was higher than in normal pregnancies (6394 and 2402, respectively, p <0.001) The sFlt-1/PIGF ratio in IUGR cases compared to normal pregnancies was significantly higher (103.6 versus 5.20, p <0.001) (Table VII. 24).

Table VII.25. Perinatal and neonatal outcomes in the IUGR group and control group

Results	**IUGR group; N=37**	**Control group; N=37**	**Statistical tests used**	**P**
VG at birth	37 [33.5-38]	38[38-39]	Mann Whitney test	<0.001
Mode of delivery (natural or cesarean)	31/37 (54.4%)	26/37(45.6%)	Fisher test	0.39
Categories: SGA, AGA, LGA (SGA - pathologic)	22/37	0/37	Fisher test	<0.001
Sex (female)	20/37	20/37	Chi-square test	0.09
APGAR score <7, at 5 min	9/37 (75%)	3/37 (25%)	Chi-square test	0.058
Meconium-stained amniotic fluid	5/37 (55.6%)	4/37 (44.4%)	Fisher test	0.9
pH <7 in the umbilical cord	1/37	0/37	Fisher test	0.99
Need for neonatal intensive	11/37 (73.3%)	3/36**(26.7%)	Chi-square test	0.37
Number of days in neonatal intensive care	32.55+/-26.546	11,5+/-7.141	Fisher test	0.40
Respiratory distress: severe/moderate/mild	15/37	6/36**	Fisher test	0.03
Intraventricular hemorrhage	6/37	2/36	Fisher test	0.15
Necrotizing enterocolitis	7/37	0/36	Fisher test	0.005
Hypoglycemia	4/37	2/36	Fisher test	0.61
Hyperbilirubinemia	12/37	10/36	Fisher test	0.02
Hypocalcemia	15/37	6/36	Fisher test	0.5
Patent ductus arteriosus or foramen ovale	8/37	3/36	Fisher test	0.09
Antepartum IUFD	1/37	0/37		---
HTA – IS	6/36	1/36	Fisher test	0.10
PE, E, HELLP, UPA	1/37	0/36	Fisher test	0.49

* Roher weight index was calculated using birth weight/waist x100. The percentiles on the Lubcenco and Fenton growth curves were assessed for each case, allowing the classification of cases into symmetric and asymmetric SGA (Fenton and Kim 2013; Lubchenco et al. 1963)

** A fetus from the control group died in utero from acute hemolytic anemia caused by parvovirus infection.

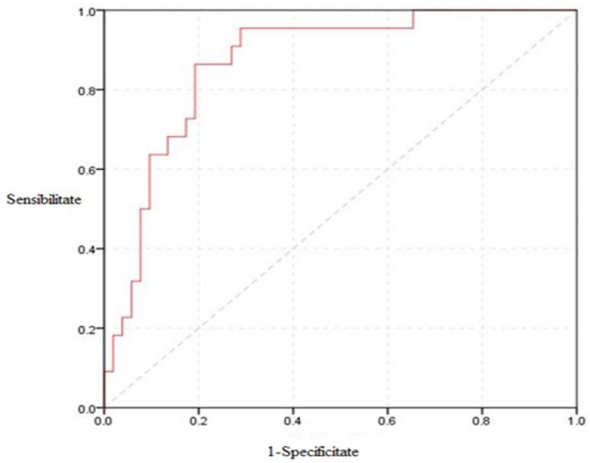

Fig. VII.36. ROC curve and cutoff value for sFlt/PlGF ratio in all study cases

The sFlt-1/PIGF ratio was considered the variable. This time all study patients were included (including those who developed PE and its complications during the current pregnancy). We found a threshold value of 36,065 with a sensitivity of 86.4% and a specificity of 80.8%, very close to that reported for PE by Zeisler: 38 (fig.VII.36).

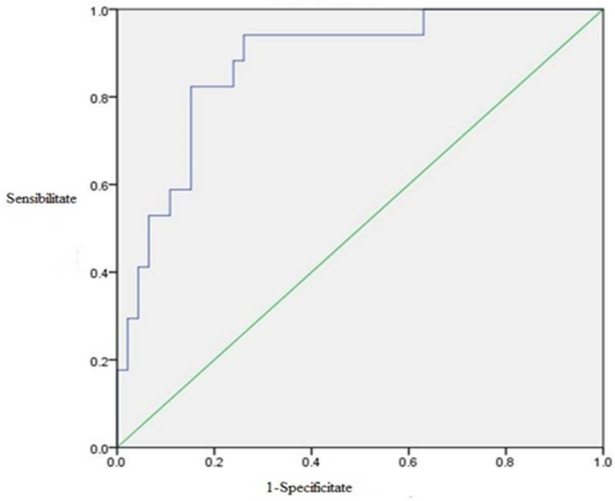

Fig. VII.37. ROC curve and cutoff value for the sFlt/PlGF ratioin the detection of IUGR cases in all study cases (except the 5 cases who developed PE, E, HELLP syndrome, UPA)

Because PE is associated with high values of the sFlt1/PIGF ratio, we recalculated the ROC curve after excluding the patients who developed hypertension - IS and its complications (PE, HELLP, UPA), namely 5 patients, 4 with PE and 1 with UPA. No cases of E or HELLP syndrome were included in our study. However, the cutoff value did not change (36,065), but a lower sensitivity (82.4%) and a higher specificity (84.8%) were recorded.

When only biometric data were used for estimated fetal risk (EFW) <10th percentile, the sensitivity was 44.4%, with a specificity of 89% for a false positive rate (FPR) of 10%. When ultrasound data and EFW <10 percentiles were combined with sFlt-1/PIGF ratio >38, the sensitivity became 84.21%, with a specificity of 84.31% for FPR of 10%.

Discussions

- ***What is the current knowledge about this topic?***

A promising approach was to determine certain serum markers in the cases suspected of IUGR at third-trimester fetal biometry, which may be useful to differentiate between SGA and IUGR. After it comes out of previous personal studies presented and from the literature, low serum PAPP-A1 levels in the first or second trimesters of pregnancy are associated with increased risk of IUGR (39,64).

Because abnormal placentation is considered to be the main cause of IUGR, a current approach is to combine fetal biometrics with indicators of placental dysfunction. Thus, the markers determined in the third trimester of pregnancy are the angiogenic factors PIGF, sFlt-1, the sFlt-1/PIGF ratio, serum endoglin, and PP1, and the hormonal factors ADAM12, hLP, and DLK (65). The reason for the use of angiogenic biomarkers is represented by placental insufficiency, which is related to impaired angiogenesis. Thus, based on this principle, in this study we assessed the role of the sFlt-1/PlGF determination in the prediction of late IUGR of vascular cause.

The practical utility of the angiogenic fraction has already been demonstrated in PE screening. Zeisler et al. showed its predictive value for preeclampsia, finding a cutoff value of 38 (63).

In our study we calculated the mean PIGF level in the group of pregnant women with IUGR, and we found it significantly lower than in the control group (86.6 vs 459.3, $p < 0.001$), (Table VII.24). In the same group of pregnant women the mean sFlt1 level was higher than in normal pregnancies (6394 vs 2402, $p < 0.001$), (Table VII.24). The results obtained are similar to those in the literature showing the differences in the expression of angiogenic and antiangiogenic factors in conditions of chronic hypoxia. Defective angiogenesis is responsible for changes in these proteins, a process demonstrated by Ahmed and his team (66).

In pregnant women with IUGR the sFlt-1/PIGF ratio, or PE fraction calculated in our study, was significantly higher than in controls (103.6 versus 5.20, $p < 0.001$), (Table VII.24).

ROC curve (fig.VII.36) analysis showed a threshold value of 36.065 with a sensitivity of 86.4% and a specificity of 80.8%, close to the threshold value for PE found by Zeisler's team - 38 (63).

Recalculating the ROC curve (fig.VII.37) after the exclusion of pregnant women with pregnancy-induced vascular pathology (HTA - IS), which could influence the results, we found that the threshold value did not change, but sensitivity was lower (82.4 %) and specificity higher (84.8%).

With this study we can confirm the role of PE fraction determination in the detection of pregnant women with IUGR (67).

There are numerous studies confirming the role of the angiogenic fraction (sFlt-1/PIGF ratio) in the detection of PE, some of them having the same threshold value of 38 as in our study (68–70).

Fewer studies have examined the role of placental angiogenic factors in predicting other adverse pregnancy outcomes due to placental insufficiency: UPA (70), IUGR (65,68,71–73), IUFD and preterm birth (71).

Many studies suggest that adding the angiogenic biomarkers to routine third-trimester ultrasound assessment and maternal risk factor analysis would improve the SGA detection rate. Thus, Bakalis er al. performed a routine newborn screening of SGA fetuses, combining maternal characteristics (maternal medical history) and fetal weight estimated by ultrasound by biometry between weeks at 30-34 weeks gestation. At a false-positive rate of 10%, in neonates delivered less than 5 weeks after assessment, they found a sensitivity of 80%, 87%, and 92%, for birth weights below the 10th, 5^{th}, and 3rd percentiles, respectively. The respective detection rates of combined screening for SGA neonates delivering ≥ 5 weeks following assessment were

57%, 64%, and 71%. When an angiogenic biomarker was added to the previously described screening, it predicted at a 10% false-positive rate, 85%, 93%, and 92% of SGA neonates delivering <5 weeks following assessment with birth weight <10th, <5th and < 3rd percentiles, respectively. The respective detection rates of combined screening for SGA neonates delivering ≥ 5 weeks following assessment were 57%, 64%, and 71%. (72,74).

Our study confirms the idea that by adding serum markers (sFlt/PlGF ratio) to ultrasound biometry the sensitivity of the screening for late IUGR detection can be increased. When we used biometry alone to estimate fetal weight below the 10th percentile, the sensitivity was 44.4% with a specificity of 89% for a false-positive rate of 10%. Subsequently, we combined the ultrasound data, EFW <10 percentiles, with the sFLT-1/PIGF ratio> 38 and obtained a sensitivity of 84.21% and a specificity of 84.31% for a RPF of 10%, for the detection of cases with IUGR.

Many studies on the role of the sFlt/PlGF ratio in the diagnosis of IUGR have not ruled out the association of other placental insufficiency-related disorders, such as PE and UPA, which may influence the results. Komwilaisak published such a study, arguing that "in daily practice, these conditions are frequently associated, so the study reflects reality and its results could be generalizable" (73).

Our study has shown that the sFlt/PlGF ratio is a useful biochemical marker in identifying cases with IUGR. Moreover, our study calculated the threshold value for it, 36.05, very close to the threshold value of 38 determined by Zeisler and his team (63) for PE detection. This value does not change when all IUGR cases are taken into account, including or excluding the cases with PE and its complications.

In this study, cesarean delivery predominates in group I (54.4%), but compared to group II (45.6%) the percentage is statistically insignificant (p = 0.39), (Table VII. 25). As there were other indications for cesarean delivery (high myopia, problems related to birth canal bony and soft tissue structures, scarring ulcer, pelvic presentation, acute fetal distress), the number of cesarean births was high in both IUGR and control groups. , so these results are not statistically significant. According to the protocol implemented by Figueras et al. the decision to deliver and also the mode of delivery is established following fetal wellbeing assessment according to gestational age by CTG and maternal-fetal Doppler (75).

The prognosis of IUGR fetuses in our studies was favorable, and no perinatal IUFD or mortality was recorded as the mean gestational age at delivery was 36 weeks, and thus the severe complications of fetal prematurity did not overlap with lesions due to chronic hypoxia (Table VII .25).

The detrimental effects of hypoxia on the fetus cannot be completely avoided, even if the compensatory mechanisms of the fetus intervene, namely the phenomenon of circulatory centralization which protects the vital organs (brain, heart, adrenals). IUGR fetuses are vulnerable as a result of prolonged chronic hypoxia or exacerbated chronic hypoxia, and any additional stress will result in brain damage with adverse repercussions and poor fetal prognosis (3,76).

The lower the gestational age, the poorer the fetal prognosis, as low gestational age associates the complications of fetal prematurity, a very important aspect in making the delivery decision. Intraventricular hemorrhage is a much more common complication when prematurity is associated, and it as well as respiratory distress can be prevented by antenatal administration of steroids (77). Although it is known that premature infants can tolerate longer periods of hypoxia-ischemia, this is only one critical period in the development of fetal brain, as subsequent lesions can alter the developmental path of the nervous system and can trigger various lesions (neuronal connectivity disturbances, apoptosis), which cannot be detected immediately. These changes can be seen by fetal MRI a few weeks after birth which reveals a decrease in white matter (78,79).

- ***What are the implications for public health practice?***

Assessment of fetal wellbeing in the third trimester of pregnancy is very important for a good fetal and neonatal prognosis.

The objective of third-trimester screening for IUGR is to identify high-risk pregnancies that require closer monitoring, referral to a level III hospital unit for a better assessment of the time of birth, but also for the care provided to newborns. in the neonatal intensive care unit.

When the sFlt/PlGF ratio> 38, the fetal IUGR is in good condition, and the Doppler circulation in the fetal territory is within the normal range, the fetal prognosis will be more favorable and the fetal and neonatal morbidity and mortality will be lower.

Determining the sFlt/PlGF ratio is also useful in more closely monitoring the cases at risk of PE, thus avoiding prolonged and unnecessary hospitalizations, stress and anxiety of risk-free pregnant women.

Conclusions

1. The sFlt/PlGF ratio is already used in current practice for diagnosing and managing PE, but it is also useful in other conditions caused by placental insufficiency, one of them being late IUGR of vascular cause;
2. According to this study we can confirm that the sFlt/PlGF ratio can be used in IUGR detection;
3. For IUGR screening, we can use the same threshold value of 38 as in PE, and the presence of an associated PE does not influence the results.
4. Through this study we confirm the idea that by determining the sFlt/PlGF ratio and the fetal biometry the sensitivity of the screening for the detection of late IUGR can be increased.

3.5. *Histopathological appearances of placenta in IUGE*

Objective and motivation of the study

The objective aim of the study was to highlight the main placental changes in IUGR.
The motivation for choosing this study was to evaluate the placental histopathological changes that occur in IUGR cases of vascular or placental cause, as it is known that placental pathology underlies most complications that occur during pregnancy (PIH, PE, E, HELLP, UPA).

Material and methods

To illustrate the histopathological appearances of IUGR, we presented a series of cases collected during the doctoral research. Twenty-five placentas from pregnant women with IUGR were histopathologically assessed, and the findings were presented in this study.

To examine the histopathological specimen we followed the protocol for processing surgical specimens. He was accompanied by the patient's medical record including his/her data and the presumptive diagnosis. The thus processed histopathological specimens allowed the correct interpretation of the lesions and thus an anatomopathological diagnosis. The histopathological examination of the placentas was performed by the team of pathologists at the Laboratory of Pathological Anatomy of the Iasi "Cuza Voda" Maternity.

I also conducted a literature search using PubMed and specific terms, (intrauterine growth restriction, placenta, placental pathology, placental vascular lesions, villitis, placental infarction, spiral arteries, trophoblast invasion) and studied the specialized literature in order to confirm the role of anatomopathological study of the placenta in IUGR.

Results

By examining the 25 placentas of IUGR neonates we found a diversity of histopathological lesions from minimal to severe lesions.

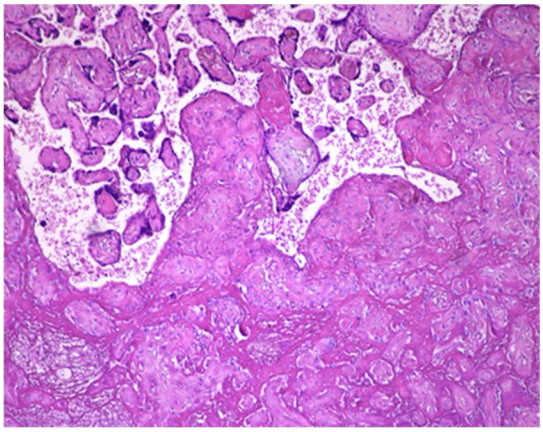

Fig. VIII.45. Chronic infarct on the background of distal villous hypoplasia (HEx10).

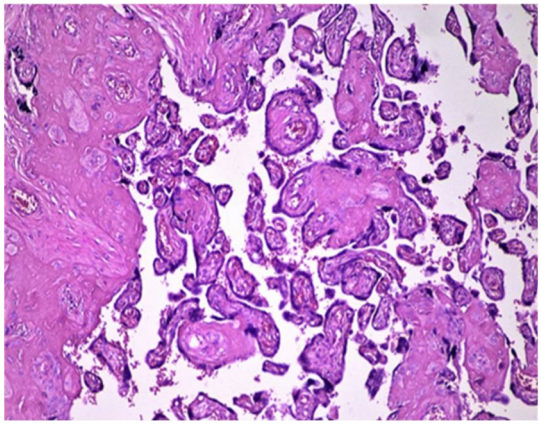

Fig. VIII.47. Fibrinoid areas that include intermediate trophoblast cells, intravillous fibrinoid (HEx10)

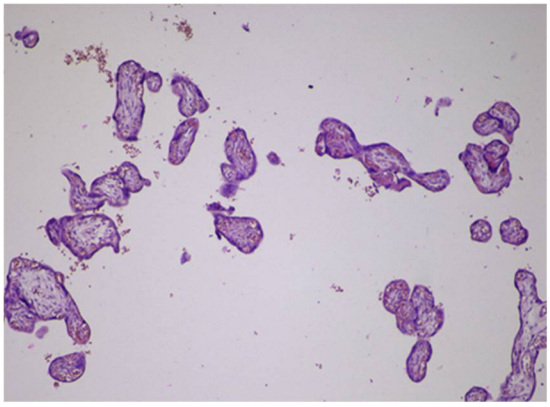

Fig. VIII.49. Distal villous hypoplasia (HEx10)

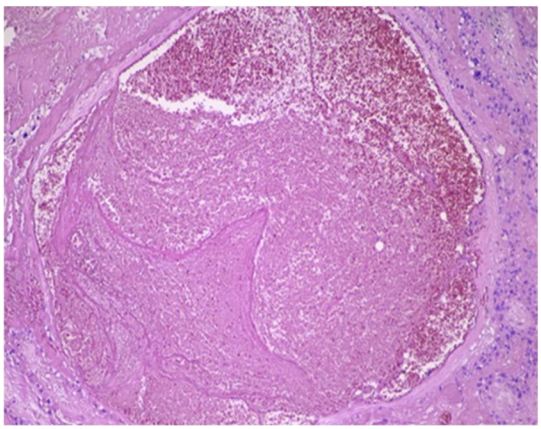

Fig. VIII.61. Parietal vascular thrombosis (HEx10)

Discussions

The placenta, which is richly vascularized, plays an important role in the development of IUGR. Placental ischemia, which causes placental insufficiency due to deficient uteroplacental perfusion, is the most common cause of IUGR,.

The clinical features of ischemic placental disease are detected during the second half of pregnancy, even though the pathophysiological processes that initiate the disease occur in the first half of pregnancy (80).

The histopathological changes may provide a pathophysiological explanation specific to IUGR. Histopathologically, in a normal placenta the integrity of the syncytiotrophoblast is crucial for maternal-fetal exchanges. If there is a connection defect at this level, an abnormal arrangement of trophoblastic cells occurs around the villi thickening the fetal-maternal membrane. These changes cause hypoperfusion and possibly ischemia. As a result of these changes, there is an imbalance between the processes of proliferation and apoptosis of syncytiotrophoblast cells, resulting in accumulations of nuclei of the degenerated syncytiotrophoblast, which form syncytial knots. Iskender-Mazman has shown that syncytial knots are more common in the placenta of fetuses with IUGR (81).

Since histopathological examination is performed after birth, and during pregnancy the consequences of placental lesions are detected by maternal-fetal Doppler study, histopathological examination of the placenta at IUGR pregnancies is important for determining the prognosis of subsequent pregnancies (22). There are not very accurate figures on the recurrence rate in the literature (20) because placental lesions in IUGR pregnancy are numerous and nonspecific. The recurrence rate is not relevant because the histopathological lesions had not also been studied in the miscarried or stillborn babies during trimesters I and II by the followed-up women. Thus, a recurrence rate of 17% (82) for lesions of villitis of unknown etiology and of 80% for chronic histiocytic intervillositis (83) are reported in the literature.

From a histopathological point of view, in normal full-term pregnancy the placenta may present infarct areas of less than 3 cm located in the placental periphery, without pathological significance. Contrary to this finding, an infarct area larger than 3 cm and located in the central area, or multiple small infarcts are pathological lesions that reduce the functional surface of the placenta, resulting in the occurrence of IUGR (20). A retrospective study by Vinnars et al. in 157 PE cases showed that in 39.7% of cases with severe PE more than 5% of the placental surface had infarct lesions compared with 17.1% of the cases with moderate PE (19).

A high frequency of infarct lesions was also found in the placentas from our cases (fig.VIII.45). The extensive and multifocal nature of the lesion may be associated with IUGR (20,84).

Severe thrombotic lesions in the fetal circulation were also present in our study in stillborn fetuses. The histopathological examination of the placenta revealed: old, multiple placental infarcts; parietal thrombosis of chorionic vessels (fig.VIII.61); excessive perivillous fibrinoid deposition in the chorionic and basal plate. Normal-appearing umbilical cord consisting of two arteries and one vein but included in the edematous myxoid matrix. These multiple and old infarct areas probably occurred repeatedly during pregnancy, at different times excluding functional placental portions from function and thus affecting fetal growth and wellbeing (85). For these reasons it can be said that the placenta is *a diary of intrauterine life*.

Fibrinoid accumulations described in most of our study cases are histopathological changes associated with IUGR pregnancies, findings also described in the literature. These reflect a fetal adaptation process to placental insufficiency (81.86).

Fetal thrombotic vasculopathy can be the cause of neonatal cerebral palsy or other forms of fetal neurological impairment and is all the more severe as lesions of acute hypoxia overlap during labor. Phenomena of neurological impairment in the immediate postpartum or the first

years of life are present in 52-65% of newborns (21). The presence of fetal thrombotic vasculopathy detected on anatomopathological examination of the placenta implies:

• closer monitoring of the newborn for neurological disorders;

• a full-term newborn showing no neurological impairment but with severe placental lesions requires long-term neurological monitoring;

In situations of severe perinatal asphyxia, it is important to know the preexisting placental lesions as these cases can become forensic cases (21).

The anatomopathological examination of the placenta is important and should be part of the testing aimed at identifying the causes of IUGR. As this examination can only be done after delivery, imaging methods are those that can highlight, during pregnancy, the consequences of vascular changes due to abnormal placentation.

No histopathological changes specific to IUGR pregnancy have been described, but it is known that the most common lesions are placental infarction, calcium deposits, and fibrinoid accumulations (56,81,86). The fact that these lesions occur and normally full-term pregnancy demonstrates that placental maturation is accompanied by various nonspecific histopathological changes, which can only endanger fetal growth when they occur early and spread over a large placental surface.

Conclusions

1. IUGR occurs as a result of a complex placental pathology;
2. There is not a single specific lesion that can cause IUGR
3. Anatomopathological examination of the placenta can establish the long-term neurodevelopment outcome of the newborn IUGR, but also the prognosis of subsequent pregnancie;
4. Anatomopathological examination of the placenta can be for the attending physician an essential component of autopsy in cases of intra- or peripartum fetal death.

General conclusions

1) First-trimester screening by highlighting the maternal risk factors, MBP, determination of biochemical markers (PAPP-A1, MPV) and biophysical markers (UtA-PI) is essential in highlighting pregnancies at risk of PE and/or IUGR of vascular cause, and involves the initiation of prophylactic treatment with Aspenter to reduce fetal and neonatal morbidity and mortality;
2) The value of the sFlt-1/PlGF ratio can be used in screening pregnant women at risk of PE to assess the severity of PE and short-term prediction of pregnancy duration and risk of premature delivery;
3) Our study supports the idea that the addition of angiogenic biomarkers (sFlt1/PIGF ratio) to ultrasound biometry may increase the sensitivity of screening for late IUGR;
4) The use of Delphi criteria for defining IUGR is very important, as the timely recognition of a fetal IUGR improves both the management and the neonatal outcomes;
5) The use of all methods for the diagnosis and assessment of wellbeing of IUGR fetuses allows the elucidation of false-positive diagnostic situations, thus avoiding the extraction of a healthy premature fetus and also a prolonged and risky keeping of the IUGR fetus in a hostile hypoxic intrauterine environment.;
6) Histopathological examination of the placenta confirmed that placental lesions in pregnancy IUGR are not specific and include a wide range of lesions, from minimal changes to severe vascular lesions that affect fetal growth and wellbeing.

Achieving the general and specific objectives

The general objectives of the thesis have been met - the epidemiological data, behavioral factors, associated or pregnancy-related diseases, and components of fetal wellbeing monitoring elements were all assessed in our study cases, this way the risk factors for IUGR being identified, and the adequate management of at-risk cases being established. We also made various correlations between risk factors and the occurrence of SGA or IUGR.

The specific objectives of the thesis have been met by demonstrating that thorough first-trimester history taking as well as PAPP-A1, MBP, and UtA-PI determinations are early markers for IUGR. We have also demonstrated the role of Aspirin administered in the first trimester of pregnancy in reducing fetal and neonatal morbidity and mortality, and also that the sFlt/PlGF ratio can be used as a diagnostic marker for late IUGR of vascular cause.

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