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Morphological characteristics of placentas associated with idiopathic intrauterine growth retardation: a clinicopathologic study

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ABSTRACT

Objectives: To investigate histopathologic findings, placental diameters and characteristics of syncytial knots in the placentas from idiopathic intrauterine growth retardation (IUGR) pregnancies, and to compare them with a normal birth weight group.

Study design: Based on strict eligibility criteria, this prospective case–control study included 52 term placentas from idiopathic IUGR pregnancies and 69 term placentas from normal birth weight pregnancies. The study was carried out at the Clinical Hospital Centre, Split, where all placentas were collected and examined. For each placenta, diameters were measured and the following histopathologic findings were recorded: infarction, intervillous thrombosis, abruption, villous branching and maturation, chorioamnionitis, decidual vasculopathy and hemorrhagic endovasculitis for each placenta. In addition we assessed quantitative (number of syncytial knots and number of syncytial nuclei per syncytial knot) and qualitative (density and surface area) characteristics of syncytial knots in each placental sample. Statistical significance was tested using χ^2-test, Student's *t*-test and Mann–Whitney *U*-test. Statistical significance was set at $P \leq 0.05$.

Results: There was no difference in investigated histopathologic findings between idiopathic IUGR placentas and control group placentas. Placental diameters correlated significantly with neonatal birth weight ($r = 0.64$; $P < 0.01$); with higher birth weight there is an increase in placental diameters. Syncytial knots from idiopathic IUGR had significantly smaller surface area ($Z = 2.637$; $P = 0.008$) and higher density ($Z = 3.225$; $P = 0.001$) compared with the control group, while there is no difference in number of syncytial knots per individual villus, total number of syncytial knots in each placenta sample or number of syncytial nuclei per syncytial knot.

Conclusions: The investigated histopathologic findings in idiopathic IUGR placentas are incidental, with no higher frequency than in placentas from uncomplicated pregnancies, and should not be considered as possible causative factors for idiopathic IUGR. The demonstrated qualitative changes of syncytial knots in placentas associated with IUGR could represent a compensatory mechanism.

1. Introduction

Intrauterine growth retardation (IUGR) is usually defined as a birth weight below the 10th percentile for gestational age [1]. It has a significant impact on perinatal mortality and morbidity, affecting approximately 7–15% of pregnancies [2,3]. Pre-existing maternal diseases, hypertensive disorders of pregnancy and various antenatal acquired infections are considered to be risk factors and can cause IUGR. However, in most cases IUGR remains idiopathic and represents a serious clinical problem.

In recent years, it is firmly believed that research on the placenta holds the key to better understanding of IUGR etiology. Placentas from IUGR are in general smaller. A number of studies have reported decreased weights, volumes and placental diameters in placentas associated with IUGR, as compared with normal birth weight groups [4–6]. Histopathologic findings such as infarctions, thrombosis and calcifications can be seen, but none of them are pathognomonic for idiopathic IUGR alone [7,8]. Furthermore, these findings are more common when IUGR is associated with previously mentioned hypertensive disorders of pregnancy, pre-eclampsia in particular [9,10].

Apart from gross anatomy and histopathologic findings of IUGR placentas, numerous studies have been focused on individual placental components such as syncytial knots. Although these

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structures were first described by Tenney and Parker in 1940 [11], no exact definition of syncytial knots has been offered to date. The general opinion is that they represent a multilayered group of syncytial nuclei that bulge only slightly on the trophoblast surface of the villi [12]. The origin of syncytial knots is also vague. Some authors consider them to represent accumulation of aged, dying nuclei, products of programmed cell death also called apoptosis, and the final step in trophoblast turnover [13,14]. Burton and Jones think that syncytial knots normally accumulate on the villous surface until term, without any correlation to apoptosis or trophoblast turnover [15]. Several studies found an increase in the number of syncytial knots in placentas from pregnancies complicated by pre-eclampsia, IUGR and hypoxic conditions [14,16]. However, none of those studies described characteristics of syncytial knots from idiopathic IUGR alone, which urged us to look into this subject more diligently.

The aim of the present study was to investigate histopathologic findings, placental diameters and characteristics of syncytial knots in placentas from idiopathic IUGR pregnancies, and to compare them with a normal birth weight group.

2. Materials and methods

2.1. Study patients

Our study was designed as a prospective case–control study. In order to compare pregnancies complicated by idiopathic IUGR and normal pregnancies, 70 term placentas from uncomplicated pregnancies and 70 term placentas from pregnancies complicated by idiopathic IUGR were analyzed. Newborns with birth weight below the 10th percentile according to national standards developed at Split University Hospital Center, where the study was performed, were considered as IUGR cases [17]. Strict eligibility criteria were set to separate idiopathic IUGR from IUGR associated with different disorders of pregnancies (Table 1). Eighteen placentas from the idiopathic IUGR group and only one from the control group did not fulfill the eligibility criteria, so the total number of placentas in the idiopathic IUGR group was 52 and in the control group was 69.

The local Ethics Committee gave approval for this study and all participants provided informed written consent. The study was conducted in accordance with the Code of Ethics of the Declaration of Helsinki.

2.2. Preparation of placental tissue and histopathologic examination

Placentas were collected from the delivery room within 20 min of vaginal delivery. They were fixed in 10% formalin and referred to the Department of Pathology for analysis. After gross examination, placental diameters were recorded along two axes, perpendicular to each other, by means of measuring tape. Placental samples were obtained by standard procedure: one section from the umbilical cord and membranes, and two sections from macroscopically normal placental disk (one close to the umbilical cord insertion, and the other midway between cord insertion and placental margin). All macroscopically detected focal changes in the placentas were sampled. To assess characteristics of syncytial knots, an additional placental section was obtained close to the umbilical cord insertion and distant from any pathologic areas seen macroscopically. Those samples contained the center of the placental lobule, chorionic plate and decidual floor. Placental sections were embedded entirely in paraffin, cut into 4 μm thick sections, mounted on silanized slides and dried at 37 °C. Finally, sections were stained with hematoxylin and eosin (H&E). The following histopathologic variables were evaluated: infarction, intervillous thrombosis, abruption, villous branching and maturation, chorioamnionitis, decidual vasculopathy (including acute atherosis and fibrinoid necrosis) and hemorrhagic endovasculitis. Abruption was diagnosed clinically or on gross examination as a retroplacental blood clot, or histopathologically as parenchymal indentation with decidual and parabasal hemorrhage. Villous branching and maturation were assessed according to gestational age as adequate or inadequate. All placentas were macroscopically and histologically examined by the same perinatal pathologist blinded to the assigned clinical category.

2.3. Assessment of syncytial knot characteristics

The syncytial knot was defined as a multilayered aggregation of at least 10 syncytiotrophoblast nuclei protruding from the villous surface that was not in direct contact with adjacent villi [18]. All measurements were performed manually using a 40× objective (Olympus BX41 microscope). Each placental sample was analyzed per 10 fields of view. Syncytial knots were expressed as the number of syncytial knots per individual villus and as the total number of syncytial knots in each placental sample. In addition, syncytial nuclei were counted in each syncytial knot. The surface area of each syncytial knot was determined using the Cell D1 Image analysis program (Olympus) (Fig. 1). The ratio between the number of syncytial nuclei in each syncytial knot and its surface area was considered to be its density.

2.4. Statistical analysis

Statistica 7.0 software was used for data analysis. The Kolmogorov–Smirnov test was used to determine whether data

Table 1
Eligibility criteria for the study.

	Comment
Inclusion criteria	
Clinical diagnosis of IUGR	Birth weight below 10th percentile according to sex, gestational age and maternal parity
Singleton term pregnancy	37–42 weeks of gestation
Apgar score 8 and over	APGAR score taken in the first minute after birth
Umbilical cord blood pH > 7.2	
Exclusion criteria	
Neonatal malformations	
Clinical signs of pre-eclampsia	Systolic blood pressure >140/90 mm Hg; significant proteinuria >300 mg/L/24 h
Clinical signs of intra-amniotic infection syndrome	Body temperature during delivery >37.5 °C; fetal tachycardia on cardiotocogram with basic frequency >160/min
Laboratory signs of intra-amniotic infection syndrome	Leukocytes $>16 \times 10^9$/L; CRP >10 mg/L
Maternal anemia	Hemoglobin <100 g/L
Laboratory signs of HELLP syndrome	Platelets $>100 \times 10^9$/L; AST or ALT >70 U/L; LDH >600 U/L
Enhanced activity of coagulation system	Fibrinogen <2 g/L; D-dimers >400 mg/L