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● *Original Contribution*

EVALUATION OF PLACENTAL MICRO-VASCULARIZATION BY SUPERB MICRO-VASCULAR IMAGING DOPPLER IN CASES OF INTRA-UTERINE GROWTH RESTRICTION: A FIRST STEP

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Abstract—Superb micro-vascular imaging (SMI) Doppler has proven to be a valid method to assess normal placental micro-vascularization. In this study, we present the application of SMI Doppler to assess placental micro-vascularization in cases of placental insufficiency. We observed fewer secondary and tertiary villi in cases of intra-uterine growth restriction, as well as a lower pulsatile index of secondary villi. The observations made in our study stress the diagnostic potential of SMI Doppler in placental insufficiency. (E-mail: jsainz@us.es) © **2021 World Federation for Ultrasound in Medicine & Biology. All rights reserved.**

Key Words: **SMI Doppler, Intra-uterine growth restriction, Placental micro-vascularization, placental insufficiency.**

INTRODUCTION

Placental dysfunction is related to pregnancy complications such as intra-uterine growth restriction (IUGR) or pre-eclampsia (Figueras and Gratacos 2017), and its weight is known to influence the perinatal outcome (Figueras et al. 2018; McCowan et al. 2018).

Currently, we use uterine arteries and fetal Doppler measurements, including middle cerebral artery, umbilical artery (UA) and ductus venosus, for monitoring and managing IUGR cases. However, these cases have quite limited diagnostic and predictive capabilities for adverse outcomes in instances of late-onset IUGR, which is diagnosed after 32 wk (Figueras et al. 2018). Thus, new monitoring methods are needed for a proper clinical management in these cases. Some authors have attempted to assess placental vascular flow using 3-D power Doppler ultrasound (Mercé et al. 2004; Campbell 2007; Eastwood et al. 2018) or ultra-fast Doppler (Tanter and Fink 2014), which have their own limitations (Jones et al. 2009; Martins et al. 2012).

In this regard, there are new promising techniques such as superb micro-vascular imaging (SMI) Doppler, which employs a unique algorithm to eliminate motion artifacts and signals from overlaying tissue (Machado et al. 2016). This allows the capture of low-velocity blood flow vessels, rendering it an ideal tool for assessing placental micro-vascularization. Hasegawa and Suzuki (2016) were the first to use SMI Doppler during pregnancy to obtain images of a placental infarction, and others have applied this technique to describe the vascularization of normal placental and fetal organs (Hasegawa et al. 2018; Mack et al. 2019).

Recently, our group published a study describing normal placental Doppler patterns throughout pregnancy using SMI Doppler, showing that this technique is a valid method to assess normal placental micro-vascularization (Sainz et al. 2020). Our next objective is to apply this technique to evaluate pathologic pregnancies. In this study, we present the application of SMI Doppler for determining placental micro-vascularization in situations of placental insufficiency.

MATERIALS AND METHODS

Patients

This study recruited 16 pregnant women who belonged to one out of four different scenarios described below. Patients had a low-risk result for combined first trimester screening, and no morphologic abnormalities were found during the second trimester scan.

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Normal pregnancies. Five women were 35−37 wk pregnant with normal gestational development. Five healthy newborns were born at term, weighing between 3320 g and 3970 g, with Apgar scores above 7 at 1 and 5 min and a mean umbilical cord blood pH of 7.26.

Small for gestational age. Four women who were 37−38 wk pregnant met the criteria for small for gestational age (SGA). Estimated fetal weight (EFW) was below the 10th percentile, and fetal Doppler assessment was normal in all cases. Deliveries took place at term, with newborns weighing between 2650 and 3005 g. The 1 and 5 min Apgar scores were above 7, and the mean umbilical cord blood pH was 7.30.

Late IUGR. Four women who were 34−37 wk pregnant met the criteria for late IUGR. EFW was below the third percentile in two cases and below the 10th percentile with a pathologic Doppler assessment in the other two cases. Pregnancies ended at term, with newborns weighing between 2530 g and 3000 g. Apgar score at 1 and 5 min were above 7, and the mean umbilical cord blood pH was 7.27.

Early IUGR. Three pregnant women met the criteria for early IUGR at 25, 26 and 29 wk. EFWs were 435 g, 558 g and 1009 g, respectively, all below the third percentile. Fetal Doppler assessment was pathologic (Pulsatility index [PI] of the middle cerebral artery and cerebroplacental ratio below the fifth percentile; PI of the UA, ductus venosus and UtA above the 95th percentile). Cytogenetic analysis of the amniotic fluid revealed no abnormalities. Intra-uterine fetal death occurred at 30 wk in one case, with a fetal weight of 560 g. The other two pregnancies ended at 28 and 30 wk with newborns weighing 435 g and 986 g. Apgar scores were above 7, and the mean umbilical cord blood pH was 7.25.

Ultrasound assessment

Expert fetal ultrasound examiners performed a placental ultrasound assessment using a Canon Aplio 500 ultrasound (Toshiba Medical Systems Corp., Tokyo, Japan) with a PUT-675 MV-3-D probe. The study protocol was reviewed and approved by the Ethics Committee of Valme University Hospital (1001-N-18), and informed consent was obtained from all patients. Following the technique described in our previous study, we applied SMI Doppler in the central part of the placenta and performed a qualitative assessment, evaluating the amount of secondary and tertiary villi. Next, we performed a quantitative assessment, evaluating the following parameters: PI and peak systolic velocity of the chorionic plate, the basal plate and the primary, secondary and tertiary villi (Sainz et al. 2020) (Fig. 1).

Anatomopathologic examination

Post-delivery placentas were submitted for anatomopathologic examination based on the latest international description in the Amsterdam Placental Workshop Group Consensus Statement (Khong et al. 2016) to identify pathologic patterns frequently found in placentas from pregnancies complicated by IUGR (Mifsud and Sebire 2014).

Statistical analysis

Numeric variables were described as means and standard deviations. Comparisons between study groups were performed using Mann-Whitney U-test for non-normally distributed data. Significance level was set at $p < 0.05$. The data analysis was performed with the statistical package IBM SPSS statistics 22 (IBM, Armonk, NY, USA).

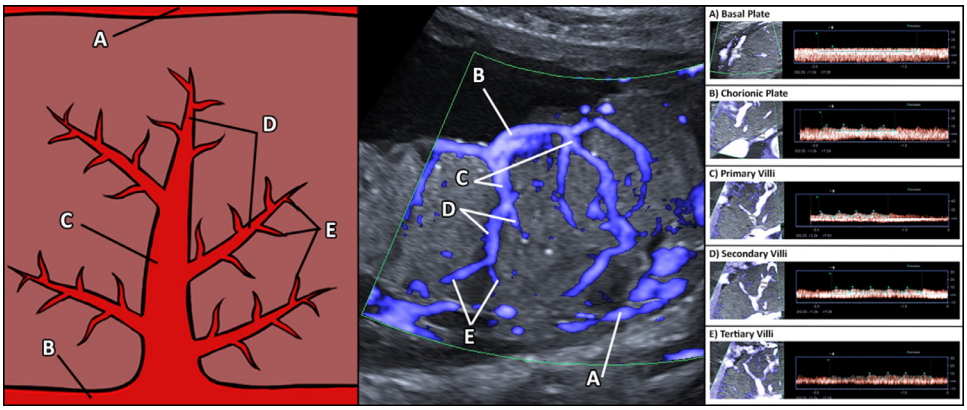

Fig. 1. Left: Outline of the functional unit, the chorionic villus, in a normal placenta. Center: Caption of SMI Doppler ultrasound assessment of the chorionic villus in a normal placenta. Right: Captions of SMI Doppler ultrasound assessment of the five components of the functional unit in a normal placenta. Each caption is presented with the waveform obtained by spectral Doppler at its right. (a) Basal plate; (b) chorionic plate; (c) primary villi; (d) secondary villi; (e) tertiary villi. SMI = superb micro-vascular imaging.

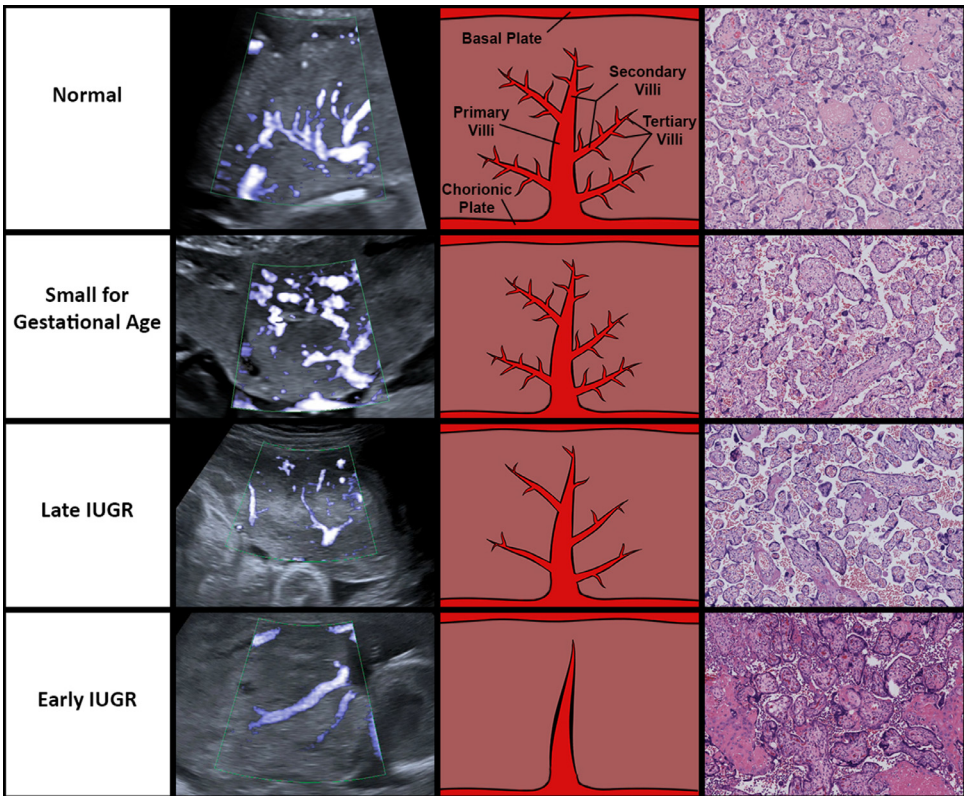

Fig. 2. Left: Captions of SMI Doppler ultrasound assessment. Center: Outline of the functional unit. Right: Captions of anatomopathologic examination. SMI = superb micro-vascular imaging.

RESULTS

The results obtained from the qualitative ultrasound assessment and pathologic examination are shown in Figure 2. It also shows an outline of the placental vascular branching, or lack thereof. We observed that normal pregnancies and SGA had a high amount of secondary and tertiary villi with a complete placental vascular branching. In cases of late IUGR, placental vascular branching could be seen with fewer tertiary villi. However, the early IUGR showed no vascular branching, and only the primary villi were observed with an almost complete lack of secondary and tertiary villi.

During anatomopathologic examination, placentas from normal pregnancies showed adequate villous maturation and a normal percentage of syncytial knots. SGA and late IUGR placentas showed similar findings. In contrast, early IUGR placentas showed accelerated villous

Table 1. Quantitative evaluation of placental parameters evaluated by SMI doppler

	Normal	SGA	Late IUGR	Early IUGR
Pulsatile index				
Basal plate	0.65 ± 0.19	0.44 ± 0.23	0.36 ± 0.11	0.38 ± 0.17
Chorionic plate	0.89 ± 0.07	0.46 ± 0.08	0.49 ± 0.05	0.95 ± 0.66
Primary villi	0.82 ± 0.05	0.66 ± 0.17	0.63 ± 0.22	0.56 ± 0.05
Secondary villi	1.25 ± 0.12	0.65 ± 0.17	0.5 ± 0.14	-
Tertiary villi	1.38 ± 0.19	0.73 ± 0.22	0.64 ± 0.18	-
Peak systolic velocity*				
Basal plate	18.68 ± 5.33	13.6 ± 5.64	11.98 ± 5.76	11.5 ± 1.6
Chorionic plate	17.6 ± 2.51	9.25 ± 1.92	12.8 ± 2.86	8.67 ± 0.31
Primary villi	13.88 ± 0.64	13.35 ± 4.74	10.7 ± 5.64	10.27 ± 0.31
Secondary villi	10.62 ± 0.94	9.58 ± 2.8	8.63 ± 2.89	-
Tertiary villi	11.4 ± 1.23	7.25 ± 1.63	8.85 ± 1.1	-

IUGR = intra-uterine growth restriction; SGA = small for gestational age; SMI = superb micro-vascular imaging.
Results are given as mean and standard deviation. Values marked by the same letter showed statistically significant difference.
* Expressed in cm/seg peak systolic value.

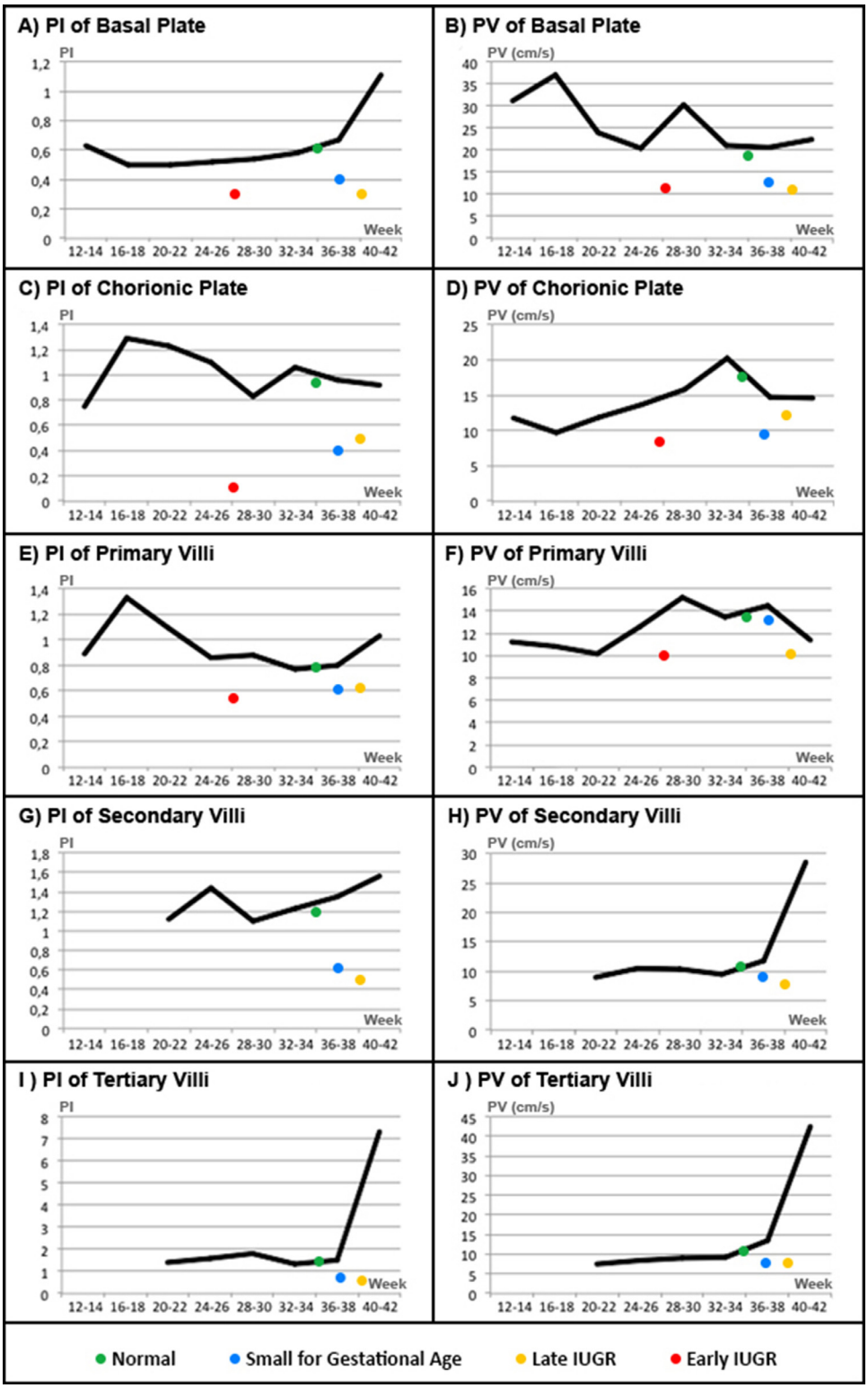

Fig. 3. Quantitative evaluation of placental parameters evaluated by SMI-Doppler. Mean values with reference curves. PI = pulsatile index; PV = peak systolic velocity; SMI = superb micro-vascular imaging.

Table 2. Quantitative evaluation of placental parameters evaluated by SMI Doppler

	Normal	IUGR	*p* Value
Pulsatile index			
Basal plate	0.56 ± 0.23	0.37 ± 0.13	0.114
Chorionic plate	0.70 ± 0.24	0.69 ± 0.45	0.758
Primary villi	0.75 ± 0.14	0.60 ± 0.16	0.114
Secondary villi	0.98 ± 0.35	0.50 ± 0.14	0.034
Tertiary villi	1.09 ± 0.39	0.64 ± 0.18	0.051
Peak systolic velocity*			
Basal plate	16.42 ± 5.76	11.77 ± 4.19	0.091
Chorionic plate	13.89 ± 4.89	11.02 ± 2.99	0.351
Primary villi	13.64 ± 2.95	10.51 ± 4.00	0.071
Secondary villi	10.16 ± 1.64	8.62 ± 2.90	0.330
Tertiary villi	9.56 ± 2.56	8.85 ± 1.13	0.604

IUGR = intra-uterine growth restriction; SMI = superb micro-vascular imaging.

Comparisons between normal and IUGR placentas. Results are given as mean and standard deviation.

* Expressed in cm/seg peak systolic value.

maturation, and a high percentage (33%) of syncytial knots for gestational age. They also showed signs of villitis and maternal and fetal vascular malperfusion, with avascular distal villi, central vascularization and a reduced vasculo-syncytial membrane. There were also signs of acute chorioamnionitis and villitis in these cases.

Table 1 shows the results obtained from the quantitative ultrasound evaluation. In Figure 3, these results are shown in relation to the reference curves developed by our group. We observed a decrease in most of the parameters evaluated in cases of placental insufficiency, especially in early IUGR (Supplementary Video 1 and 2, online only). Given the lack of secondary and tertiary villi in cases of early IUGR, parameters in these vessels could not be evaluated.

Table 2 shows the comparisons of quantitative parameters between the normal and IUGR groups, including early and late IUGR. We can see differences in almost all parameters (more evident in secondary villi), with lower values in cases in IUGR.

DISCUSSION

This study is just a first approach to the study of placental micro-vascularization using SMI Doppler in cases of insufficiency. Our first observations must be seen with caution given the low number of cases in our study. In the qualitative ultrasound assessment, we observed a decrease of secondary and tertiary villi in IUGR placentas in relation to normal placentas. This was more evident in early IUGR, with an almost complete lack of secondary and tertiary villi. In contrast, SGA placentas did not show this decrease, and there were no relevant differences with normal placentas. The anatomopathologic examination revealed important findings in cases of early IUGR, with no differences between late IUGR, SGA and normal placentas. However, we know that manifestations of utero-placental flow insufficiency are usually late and often irreversible (Baschat 2001; Hecher 2001; Cosmi 2005; Turan 2008; Oros 2011), given that the alteration of the UA Doppler is seen when at least 30% of placental vases are obliterated, and at least 50% of them are if the Doppler alterations are severe (Salafia 2006).

The quantitative ultrasound assessment revealed a decrease of the parameters in relation to normal values described by our group. We start to observe these differences between normal and IUGR cases, including early and late IUGR, when evaluating the pulsatility index (IP) of secondary and tertiary villi. This decrease of placental vascular resistance may be explained by the models for the origins of fetal hypoxia (pre-placental, utero-placental and post-placental hypoxia) presented by Kingdom and Kaufman (1997). Although the power of this study is limited by its small sample size and the absence of ultrasound and pathologic study quantitative correlation, and thus, the evidence is not enough to draw any firm conclusions, the observations made in this study suggest that Doppler values in cases of placental insufficiency might differ from normal placentas. Moreover, it raises the question of differences existing between pathologies.

Currently, we differentiate late IUGR, which is diagnosed after 32 wk, from early IUGR (Gordijn et al. 2016). Early IUGR shows an increase in blood flow resistance in the UA, which is associated with higher perinatal mortality rates and worse maternal and perinatal outcomes (Savchev et al. 2014). In late IUGR, placental insufficiency is often not detected by Doppler evaluation, which makes the assessment of SGA fetuses challenging (Soothill et al. 1999). Although SGA was once considered a benign entity, we now know that this group encompasses not only constitutionally small fetuses but also a significant number of late-onset IUGR with a normal Doppler evaluation (Savchev et al. 2012), meaning that these groups are at risk of adverse perinatal outcomes (Hershkovitz et al. 2000; Van Wyk et al. 2012).

This emphasizes the importance of correctly identifying late IUGR when assessing SGA fetuses, given the clinical implications. However, although there is a large number of articles regarding IUGR placentas (Kovo et al. 2013; Mifsud and Sebire 2014), there is a surprising lack of literature for SGA placentas. This group is more common than early-onset forms and is an important source of perinatal morbidity related to placental insufficiency and of perinatal mortality altogether (Unterscheider et al. 2014; Mendez-Figueroa et al. 2016; Paz Levy et al. 2017; Walfisch et al. 2017).

Given the clinical significance of this particular entity and its pathogenesis, investigation in this field is still scarce. Our study presents an important limitation to obtain firm conclusions, but the observations made in

our study stress the diagnostic potential of SMI Doppler in situations of placental insufficiency, which might provide a basis for future studies.

Conflict of interest—The authors have not conflict of interest.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ultrasmedbio.2021.01.029.

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