CLINICAL ARTICLE

Examination of placental three-dimensional power Doppler indices and perinatal outcome in pregnancies complicated by intrauterine growth restriction

András Molnár [a,*,1], Andrea Surányi [a,1], Tibor Nyári [b], Gábor Németh [a], Attila Pál [a]

[a] Department of Obstetrics and Gynecology, University of Szeged, Szeged, Hungary

[b] Department of Medical Physics and Informatics, University of Szeged, Szeged, Hungary

* Corresponding author: András Molnár

Department of Obstetrics and Gynecology, University of Szeged, 6725 Szeged, Semmelweis utca 1, Hungary. Tel.: +36 62 545 499; fax: +36 62 545 711.

E-mail address: molnar.andras.1@med.u-szeged.hu

[1] These authors contributed equally

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Synopsis: Three-dimensional power Doppler ultrasonography showed that placental vascularization is reduced in pregnancies complicated by intrauterine growth restriction.

ABSTRACT

Objective: To examine placental vascularization using three-dimensional power Doppler (3DPD) ultrasonography in pregnancies complicated by intrauterine growth restriction (IUGR).

Methods: The present prospective study was conducted at the University of Szeged (Szeged, Hungary) from February 2012 to March 2013. Women with a singleton pregnancy who attended the maternity outpatient ward in the second or third trimester were enrolled consecutively. Women were divided into two groups: those with a normal pregnancy and those with a pregnancy complicated by IUGR. Three 3DPD indices—vascularization index (VI), flow index (FI), vascularization flow index (VFI)—were assessed.

Results: A total of 223 women were enrolled: 171 were in the control group and 52 in the IUGR group. Median VI was 3.7% (interquartile range [IQR] 3.2%–4.2%) in the IUGR group and 10.1% (IQR 8.6%–10.9%) in the control group (P=0.001). Median FI was 40.0 (IQR 39.7–42.5) in the IUGR group and 45.1 (IQR 44.1–53.1) in the control group (P=0.012). Median VFI was 2.2 (IQR 2.1–2.4) in the IUGR group and 4.8 (IQR 4.4–5.3) in the control group (P<0.001).

Conclusion: Placental vascularization was reduced in pregnancies complicated by IUGR.

1. Introduction

Modification of the fetoplacental circulation throughout pregnancy leads to alterations in the placental vascularization and the development of the fetoplacental unit. Intrauterine growth restriction (IUGR)—diagnosed when the fetus has an estimated weight below the 10th percentile for its gestational age [1,2]—is one of the most serious complications. Usually, it is a symptom of damaged placental function, but IUGR can be caused by maternal disease (e.g. diabetes).

Intrauterine growth restriction (IUGR) results in clinically relevant perinatal complications [3]. The clinical manifestations of IUGR depend primarily on the duration of contributing factors, and how long the fetus was affected [3].

The present study was performed to test the hypothesis that placental vascularization, which is decreased in pregnancies complicated by IUGR, is related not only to the frequency of cesarean delivery, but also to risk factors and clinical outcome. The aim of the present study was to evaluate the three-dimensional (3D) Doppler parameters of the placenta; assess the influence of gravidity, parity, and body mass index on these parameters; and evaluate the correlation between these parameters and perinatal outcomes in women with a pregnancy complicated by IUGR.

2. Materials and methods

A prospective study was conducted in the maternity outpatient ward of the Department of Obstetrics and Gynecology at the University of Szeged, Szeged, Hungary, between February 1, 2012, and March 31, 2013. Women with a singleton

pregnancy who attended the maternity outpatient ward in the second or third trimester were enrolled consecutively. Several exclusion criteria were used: multiple pregnancy; thickened (>3 mm) nuchal translucency between the start of the 11th and the end of the 13th week of pregnancy; structural or chromosomal abnormality during the fetal or neonatal period; placenta previa; self-declared intake of illicit drugs, alcohol, caffeine, or nicotine; pharmaceutical treatment for disorders of the circulatory system (e.g. treatment with oxerutins or calcium dobesilate monohydrate);systemic disease (e.g. autoimmune disease, vasculitis, hemophilia, thrombophilia, diabetes, or HIV infection);and pregnancy-related disease [4]. All participants provided written informed consent. The research protocol was approved by the university's Ethics Committee before the study started, and the study was carried out in accordance with the Declaration of Helsinki.

The women were divided into two groups: women with a normal pregnancy (control group) and women with a pregnancy complicated by IUGR (IUGR group) [2]. The diagnosis and enrollment of women affected by IUGR was based on estimated fetal weight after two-dimensional ultrasound biometry during routine screening. The 3D power Doppler (3DPD) indices were determined to evaluate the perfusion of the placenta (uteroplacental and fetoplacental blood flow [5,6]): vascularization index (VI), flow index (FI), and vascularization flow index (VFI) throughout pregnancy. The VI corresponds to the ratio of the number of color voxels to the total number of voxels; it reflects the number of blood vessels within the volume of interest (vascularity). The FI is the ratio of the number of intensity-weighted color voxels to the total number of color voxels and represents the average blood flow intensity (blood flow). The VFI is the ratio of the number of intensity-weighted color voxels to

the total number of voxels; it integrates data on vessel presence (vascularity) and number of blood cells transferred (blood flow). The values for all three indices range from 0 to 100 [6].

Two-dimensional, 3D, and color Doppler examinations were performed on the same day using a Voluson 730 (GE Healthcare, Zipf, Austria) ultrasound machine with an RAB2–5 (2–5 MHz) convex probe. We used the placental vascular sonobiopsy method as described by Mercé et al. (Figure 1) [6]. The ultrasound volumes collected were assessed by a specialist in 3D analysis (A.S.) using the Virtual Organ Computer-aided AnaLysis (VOCAL) program within 4D View version 10.4 (GE Healthcare, Zipf, Austria).

Perinatal outcomes (umbilical cord arterial pH; 1-minute, 5-minute, and 10-minute Apgar scores; birth weight; and birth length) were compared between women with and without different risk factors (decreased placental vascularization indices [VI, FI, and VFI], maternal age, pregestational body mass index, excessive weight gain, and mode of delivery). Demographic data were collected from medical records.

The statistical analysis was conducted with SPSS for Windows version 17.0 (SPSS Inc, Chicago, IL, USA). An analysis of variance (ANOVA) was carried out to examine the association of the 3DPD indices with the gravidity, parity, and pregestational body mass index (BMI). The Mann–Whitney *U* test, the *t* test, and the z-score were used to compare 3DPD indices (VI, FI, VFI); estimated fetal weight, birth weight, and birth length; the mode of delivery; the occurrence of intrauterine complications; the necessity of transfer to the neonatal intensive care unit; the Apgar scores at 1, 5, and

10 minutes; and the umbilical cord arterial pH between the IUGR group and the control group. *P*≤0.01 was considered statistically significant. A quantile regression method was used to investigate the relationship between 3DPD indices (VI, FI, VFI) and gravidity, parity, and BMI.

3. Results

A total of 223 women were enrolled: 171 were in the control group and 52 were in the IUGR group. Demographic and obstetric characteristics are shown in Table 1. Placental location and 1-minute Apgar score did not differ significantly between groups. Gravidity, parity, prepregnancy BMI, umbilical cord artery pH, and 5-minute and 10-minute Apgar scores did differ significantly (Table 1).

Women in the IUGR group had significantly lower 3DPD indices (VI, FI, and VFI) values than did the control group (Figure 2). ~~All 3DPD indices remained constant throughout pregnancy in the normal pregnancies~~. We did not manage to perform curve analysis for the rate of reduction of 3DPD indices plotted against gestational age in the IUGR group, no trend line could be fitted to the values, and there was no linear, exponential, logarithmic etc. regression found in these cases. Therefore we would like to eliminate this sentence from the section 'Results' **You say that 3DPD indices remained constant throughout pregnancy in the control group (i.e. there was no change over time), but you do not mention whether there was change over time in the IUGR group. Please add some text to explain whether indices remained constant in the IUGR group.]** ~~3DPD indices were significantly lower in different amount in IUGR group compared to normal group~~. **[Author: Please clarify what you mean in this sentence; it does not make sense as it stands. If**

you are just trying to say that 3DPD indices were lower in the IUGR group, you said that in the first sentence of this paragraph, so can this sentence be deleted? Yes, this sentence can be deleted]

Table 2 shows the comparison of vascularization indices among women with different gravidities, parities, and pregestational BMIs. Gravidity, parity, and prepregnancy BMI had no significant effect on VI, FI, VFI by quantile regression analyses (P>0.01), but there were significant differences in VI, FI, VFI between the control and IUGR groups (P<0.01).

Perinatal complications occurred among 12 (23.1%) neonates in the IUGR group and 12 (7.0%) in the control group (P=0.01). Neonatal intensive care was needed for 16 (30.8%) infants in the IUGR group and 13 (7.6%) in the control group (P=0.01).

Median length of pregnancy was 38.4 weeks (interquartile range 37.3–39.1) in the study group and 39.1 weeks (interquartile range 38.1–40.0; P=0.01). The mean birth weight was 2674.4 ± 752.1 g in the study group and 3351.9 ± 522.4 g in the control group (P=0.01). The mean birth length was 46.5 ± 3.4 cm in the study group and 49.6 ± 2.45 cm in the control group (P=0.0051).

The mean z-score for the estimated fetal weight in IUGR pregnancies measured from 30 to 38 weeks of pregnancy was –2.9, indicating that the estimated fetal weights in the IUGR group were below the average measured in the control group by nearly three times the standard deviation.

4. Discussion

The present prospective study focused on the determination of placental vascularization indices (VI, FI, and VFI) using Mercé-type sonobiopsy [6] and demonstrated that placental vascularization was reduced in pregnancies complicated by IUGR compared with normal pregnancies, confirming previous results [7–9]. However, in contrast to the previous studies [7–9], in which the authors only compared the placental vascularization in normal and IUGR pregnancies, the present study also investigated the relationship between the 3DPD indices and perinatal outcomes. The depression of 3DPD indices correlates with the elevation rate of perinatal outcomes.

Various methods for measurement of placental vascular flow in vivo have been reported. de Paula et al. [10] scanned the whole placenta with the VOCAL technique but this method could not be utilized in almost all patients at late stages of pregnancy when the high-risk problems (i.e. IUGR) develop. Guiot et al. [7] determined 3DPD indices at five different placental locations. Noguchi et al. [8] investigated the vascularization of the entire placenta by calculating average values from 9–12 spherical samples (Noguchi type placental sonobiopsy). However, neither the sampling volume nor the number of spherical samples obtained was standardized. In fact, samples from barely vascularized edges of the placenta and from better vascularized central parts were included in the calculation of average values, which might have had a considerable influence on the results obtained.

Mercé type sonobiopsy was used in the present study, because this method has been well defined and validated, and is characterized by low intraobserver and

interobserver error [6,11]. Mercé et al. [6] examined a placental volume of 3×3×3 mm^3 located at the site of insertion of umbilical cord, which is the most vascularized portion of the placenta. This method can be used not only in the first trimester, when the overwhelming majority of high-risk pregnancies has not been developed yet, but also during the second and third trimester.

There is a debate over the normal range for each of the placental vascularization indices because the results from different authors are conflicting. The present findings are consistent with the results from Guiot et al. [7] and de Paula et al. [10] who found that the placental indices remained constant throughout pregnancy. Possible explanations for the discrepancy between the results from different authors include the use of different measurement techniques, low case numbers, and lacking information on measured volumes and ultrasound equipment settings.

In the present study, the women with an IUGR pregnancy and those in the control group did not differ significantly in terms of maternal age, gravidity, parity, pregestational BMI, or pregnancy duration at the time of the examination. This finding indicates that these factors had no influence on the condition of the arteries or the extent of angiogenesis during pregnancy.

The frequency of cesarean delivery was significantly higher among women with an IUGR pregnancy than in the control group. Growth-restricted fetuses respond sensitively to stress during labor and often do not tolerate vaginal delivery; thus cesarean delivery is performed more frequently.

The 5-minute and 10-minute Apgar scores showed significant differences with regard to VI, FI, and VFI, which can be explained by poor postnatal adaptation of infants who had been growth-restricted in the uterus. Apgar scores decreased with decreasing values for all 3DPD indices. Complications such as hypothermia, hypoglycemia, polycythemia, hyperviscosity, and breathing problems emerged, and neonatal intensive care was necessary more often in IUGR cases [3]. The decrease in all three 3DPD indices was significant. The VFI was the most sensitive predictor of complications. However, we recommend use of the FI to screen for IUGR pregnancies at increased risk of perinatal complications because this parameter is minimally influenced by other factors, such as equipment settings. The FI has the lowest coefficient of variation and the lowest rate of intraobserver/interobserver errors of the three vascularization indices [7].

The present study confirms previous results [5] indicating that the placental location has no significant influence on the three placental vascularization indices. In the previous study, Guimarães Filho et al. [5] examined 283 women between 26–35 weeks of pregnancy and monitored the effect of the position of the placenta on changes in the three indices. In the present study, women with placental adhesion anomalies and morphological disorders were excluded because such pregnancies can be affected by insufficient circulation from the beginning of the pregnancy [12] and this could have influenced the findings.

In the present study, we aimed at using an appropriately validated and reproducible method for assessing placental vascularization that can be adopted in maternal care on a routine basis. Previously published ultrasonography methods cannot be applied

to general maternal care without reservations, partly because the sampling volume [7] or the placental location and the number of samples obtained [8] were not standardized. Moreover, some methods used by other authors involve visualization of the entire placenta [7–9], which is not possible in the third trimester.

In theory, the ultrasound equipment settings could have a significant influence on the values of the 3DPD indices, making it difficult to compare the findings from different studies. However, no such effect has been observed in case–control studies [7–9]. Therefore, standard machine settings were used in the present study. Volume acquisition lasted 5–15 seconds during a time when there was no fetal motion; the mother also remained as motionless as possible to avoid the display of artifacts.

In conclusion, the differences in placental vascular flow indices between normal and IUGR pregnancies can be detected easily and the findings do not depend on equipment settings. The present results also confirm a strong correlation between the extent of reduced placental vascularization and perinatal outcome in pregnancies complicated by IUGR. We recommend the use of Mercé-type placental sonobiopsy [6] for the monitoring of IUGR pregnancies so as to reduce the rate and range of perinatal complications. With the development of telemedicine, the volumetric scans from women with a pregnancy complicated by IUGR could be forwarded to experts, making the follow-up of high-risk pregnancies more objective. However, it is important to emphasize that a therapeutic conclusion can only be drawn on the basis of the complete clinical background.

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Conflict of interest

The authors have no conflicts of interest.

References

[1] de Onis M, Garza C, Onyango AW, Rolland-Cachera MF; le Comité de nutrition de la Société française de pédiatrie. WHO growth standards for infants and young children. Arch Pediatr 2009;16(1):47–53.

[2] Lausman A, McCarthy FP, Walker M, Kingdom J. Screening, diagnosis, and management of intrauterine growth restriction. J Obstet Gynaecol Can 2012;34(1):17–28.

[3] Gaudineau A. Prevalence, risk factors, maternal and fetal morbidity and mortality of intrauterine growth restriction and small-for-gestational age. J Gynecol Obstet Biol Reprod (Paris) 2013;42(8):895–910.

[4] Surányi A, Kozinszky Z, Molnár A, Nyári T, Bitó T, Pál A. Placental three-dimensional power Doppler indices in mid-pregnancy and late pregnancy complicated by gestational diabetes mellitus. Prenat Diagn 2013;33(10):952–8.

[5] Guimarães Filho HA, Araujo Júnior E, Mattar R, Da Costa LL, de Mello Júnior CF, Nardozza LM, et al. Placental blood flow measured by three-dimensional power Doppler ultrasound at 26 to 35 weeks gestation in normal pregnancies. J Matern Fetal Neonatal Med 2010;23(1):69–73.

[6] Mercé LT, Barco MJ, Bau S. Reproducibility of the study of placental vascularization by three-dimensional power Doppler. J Perinat Med 2004;32(3):228–33.

[7] Guiot C, Gaglioti P, Oberto M, Piccoli E, Rosato R, Todros T. Is three-dimensional power Doppler ultrasound useful in the assessment of placental perfusion in normal and growth-restricted pregnancies? Ultrasound Obstet Gynecol 2008;31(2):171–6.

[8] Noguchi J, Hata K, Tanaka H, Hata T. Placental vascular sonobiopsy using

three-dimensional power Doppler ultrasound in normal and growth restricted fetuses. Placenta 2009;30(5):391–7.

[9] Pomorski M, Zimmer M, Florjanski J, Michniewicz J, Wiatrowski A, Fuchs T, et al. Comparative analysis of placental vasculature and placental volume in normal and IUGR pregnancies with the use of three-dimensional Power Doppler. Arch Gynecol Obstet 2012;285(2):331–7.

[10] de Paula CF, Ruano R, Campos JA, Zugaib M. Quantitative analysis of placental vasculature by three-dimensional power Doppler ultrasonography in normal pregnancies from 12 to 40 weeks of gestation. Placenta 2009;30(2):142–8.

[11] Tuuli MG, Houser M, Odibo L, Huster K, Macones GA, Odibo AO. Validation of placental vascular sonobiopsy for obtaining representative placental vascular indices by three-dimensional power Doppler ultrasonography. Placenta 2010;31(3):192–6.

[12] Sankaran S, Kyle PM. Aetiology and pathogenesis of IUGR. Best Pract Res Clin Obstet Gynaecol 2009;23(6):765–77.

[13] Mayo Clinic. Pregnancy weight gain: What's healthy? http://www.mayoclinic.org/healthy-living/pregnancy-week-by-week/in-depth/pregnancy-weight-gain/art-20044360. Published March 4, 2014. Accessed December 11, 2014.

Figure legends

Figure 1 Mercé-type placental vascular sonobiopsy [6] and placental three-dimensional power Doppler indices. The yellow circle corresponds to the Mercé-type placental vascular sonobiopsy (a 28-mL volume that forms a part of the placenta directly at the adhesion of umbilical cord).

Figure 2 Three-dimensional power Doppler indices in the IUGR group (n=52) and the control group (n=171). Abbreviations: VI, vascularization index; IUGR, intrauterine growth restriction; FI, flow index; VFI, vascularization flow index. The boxes represent the interquartile range, with the median shown as a dotted arrow; the most extreme values are also shown.

Table 1 Demographic and obstetric characteristics.[a]

	Control group (n=171)	IUGR group (n=52)	*P* value
Age, y	31.0 (28–34)	30.0 (26–34)	0.1
Pregnancy duration at the time of ultrasonography, wk	30.4 (19.0–37.0)	31.9 (24.1–37.6)	0.1
Median length of pregnancy, wk	39.1 (38.1–40.0)	38.4 (37.3–39.1)	0.2
Gravidity			
<3	123 (71.9)	28 (53.8)	0.01
≥3	48 (28.1)	24 (46.1)	0.01
Parity [b]			
<3	110 (73.3)	21 (55.3)	0.01
≥3	40 (26.7)	17 (44.7)	0.01
Prepregnancy BMI	22.1 ± 2.5	21.9 ± 1.5	0.02
Perinatal complications	12 (7.0)	12 (23.1)	0.01
Neonatal care	13 (7.6)	16 (30.8)	0.01
Cesarean delivery	45 (26.3)	31 (59.6)	0.01
Apgar score			
1 min	8.9 ± 2.3	9.0 ± 1.4	0.12
5 min	9.3 ± 1.3	9.7 ± 0.9	0.01
10 min	9.5 ± 0.8	9.8 ± 1.0	0.01
Birth length, cm	49.6 ± 2.45	46.5 ± 3.4	0.01
Birth weight, g	3351.9 ± 522.4	2674.4 ± 752.1	0.01
Umbilical cord arterial pH	7.2 ± 0.2	6.9 ± 1.6	0.01
Placental location			
Anterior wall	97 (56.7)	29 (55.8)	0.23
Posterior wall	74 (43.3)	23 (44.2)	0.22

[a] Values are given as median (interquartile range), number (percentage), or mean ± SD.
[b] Data available for 150 participants in the control group and 38 in the IUGR group.

Table 2 Comparison of vascularization indices among women with different gravidity, parity, and prepregnancy BMI in the control group and IUGR group.

	Mean vascularization index, %		Mean flow index		Mean vascularization flow index	
	Control group	IUGR group	Control group	IUGR group	Control group	IUGR group
Gravidity	[a]	[a]	[b]	[b]	[a]	[a]
1 [c]	9.4	3.5	44.0	39.7	4.4	2.1
2 [d]	10.9	3.5	45.5	39.7	5.3	2.4
3 [e]	10.5	3.8	47.1	39.8	5.0	2.2
4 [f]	10.0	3.3	42.5	42.5	4.6	2.3
5 [g]	8.6	–	53.1	–	5.1	–
Parity	[h]	[h]	[i]	[i]	[j]	[j]
1 [d]	9.4	5.3	44.2	39.5	4.4	2.0
2 [e]	11.3	4.8	46.0	42.5	5.5	2.0
3 [f]	11.1	6.4	47.1	39.0	5.5	2.7
4	4.6	–	43.0	–	2.0	–
Prepregnancy BMI	[k]	[k]	[l]	[l]	[j]	[j]
Normal	5.4	4.8	44.7	39.9	5.1	2.2
Obese	4.0	3.4	42.3	38.6	3.5	1.6
Normal but excessive weight gain during pregnancy [m]	5.3	4.4	46.3	39.8	4.5	2.1

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); IUGR, intrauterine growth restriction.

[a] Within-group comparison *P*=0.1.

[b] Within-group comparison *P*=0.3.

[c] Control group n=67; IUGR group n=18.

[d] Control group n=56; IUGR group n=10.

[e] Control group n=31; IUGR group n=16.

[f] Control group n=14; IUGR group n=8.

[g] Control group n=3; IUGR group n=0.

[h] Within-group comparison *P*=0.012.

[i] Within-group comparison *P*=0.068.

[j] Within-group comparison *P*=0.08.

[k] Within-group comparison *P*=0.02.

[l] Within-group comparison *P*=0.28.

[m] According to guidelines from the Mayo clinic [13].