

ORIGINAL RESEARCH

Placental virtual biopsy: 3D-US hemodynamics of normal pregnancy versus gestational diabetes

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Abstract

Objectives: We used three-dimensional ultrasound with trans-abdominal Power-Doppler (3D-US PD) to determine placental vascular evolution in normal pregnancies (NP) and in insulin-dependent Gestational Diabetes Pregnancies (GDP).

Study design: We obtained 473 measurements from 43 NP at 20 weeks-40 weeks gestation and 122 measurements from 70 insulin-dependent GDP at 22 weeks-40 weeks. Standardization was achieved recording three successive placental vascular tree volumes, measuring the spherical volume between the chorionic and basal plates always under or near funicular insertion. Parameters analysed were: mean intensity of blood flow (Flow Index, FI); percentage of volume occupied by vessels (Vascularisation Index, VI); and intensity of blood flow in the volume occupied by vessels (Vascularisation-flow index, VFI).

Results: In NP, FI increased throughout early pregnancy and decreased before delivery and correlated with fetal parameters. In contrast, in GDP, FI was high from the onset, better correlated with placental parameters, and had a diagnostic cutoff value of 45, which was only found in 7% of NP at the end of the pregnancy. VI was variable and had a low diagnostic value, being related to placental parameters; VI values were significantly lower in NP ($17.4 \pm 7.4\%$) than in GDP ($21 \pm 12\%$) with a diagnostic cutoff point at 31%. In NP, FI-peak was at 32 weeks, two weeks after the VI-peak, while VFI showed no significant differences.

Conclusions: The results showed that placental blood flow (FI) was related to fetal circulation, while the percentage of vessels per volume (VI) was related to maternal circulation. 3D-US PD indicated a diagnosis of GDP for FI > 45 and VI > 30%. We also discuss the values of change in VI that predict changes in fetal FI.

Key words

Placental sonobiopsy, Placental hemodynamic, 3D-Ultrasound, Gestational diabetes, Placental virtual biopsy

1 Introduction

Gestational diabetes is a type of diabetes that only occurs during the pregnancy as a consequence of placental hyperglycaemic factors and an insufficient maternal pancreatic response to glucose overload. It has an incidence of 4%. Glucose is the main energy source of the human body, in this case, pregnant women, but also for the fetal growth. An abnormal increase of glucose is an important risk factor, for an increase of blood sugar levels may lead to a severe health problem for pregnant women and specially fetuses. The mother transfers glucose to the fetus through the placenta. The fetus of a diabetic mother increases the production of insulin due to the mother's hyperglycemia and, at the same time, produces insulin-like or somatomedine-C, which is the fetal growth factor in utero. The higher the insulin-like or somatomedine-C production, the more macrosomic the fetus. If not treated, gestational diabetes may imply a higher risk for the fetus due to: macrosomia, malformations, perinatal death and birth complications.

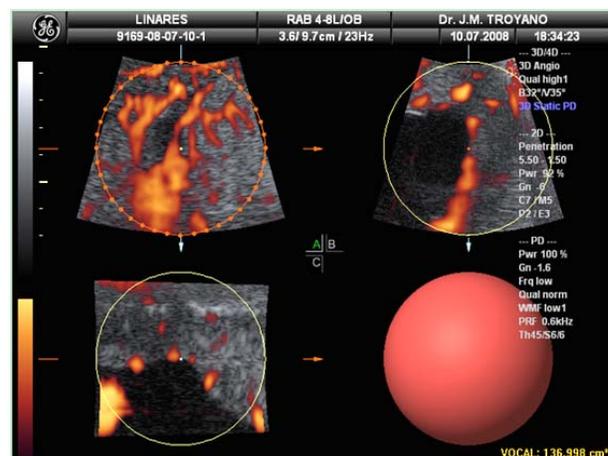
The problem with this pathology is that hemodynamic monitoring of the fetus through the umbilical blood flow does not detect its metabolic alterations early, since they are not related to its hypoxic condition. For this reason, the evaluation of conventional funicular-Doppler does not have a predictive value in gestational diabetes. However, placentas in this type of pregnancies present hystological alterations, showing a significant decrease of the number of blood vessels^[1-3]. The search for placental hemodynamic markers may be a good method for the prediction of the metabolic condition of these fetuses, no matter the degree of oxygenation, and for establishing an early prognosis^[4-7].

The placental hemodynamic study through 3D-Doppler can provide clarifying data on the vascular state of the placenta with gestacional diabetes and it may predict the future of this fetuses.

Hemodynamic measures by means of 3D ultrasound (3D-US) are highly reproducible; three-dimensional ultrasound with trans-abdominal Power-Doppler (3D-US PD) provides accurate assessment of all types of terminal vascularization^[8-10]. To study 3D flow in the vascular network of the placental complex, we applied the technique that we called virtual placental biopsy (VPB); in other words, a non-invasive 3D hemodynamic analysis of the placental vascular tissue in vivo. It is a virtual biopsy because, as already defined by one of us^[11, 12], it is performed in vivo, it is non-invasive and analyses placental tissue at a functional and anatomical level.

The VPB technique automatically provides information regarding serial volumes, grey-scale indexes and others such as VI, FI, VFI (Vascularization index or theoretical number of vessels per volume, Flow index or theoretical total flow in these vessels enclosed in the same volume of interest, and Vascularization Flow Index). It enables manual or automatic calculation of these parameters in a spherical region of interest between the chorionic and basal plates (see Figure 1).

Figure 1. Multiplanar flow study of the standardized Virtual Placental Biopsy. A. Transversal; B. Sagittal; C. Coronal. Spherical reference volume in cm^3



In general three fundamental questions must be considered during the study of 3D hemodynamic flow at the placental level: a) Regarding funicular hemodynamic events, what is their relationship with placental blood flow? b) How objective

is the assessment of villous circulation, given that placental vascular structures are a mixture of maternal inter-villous and foetal villous space? In 3D-US, we evaluate the whole placental vascular tree comprising maternal and foetal circulation. And finally. c) What is the influence of inter-villous flow on total placental flow?

The VPB map does differentiate maternal and foetal circulation, consequently, it is essential to determine whether the hemodynamic events that occur in the placenta correlate with the blood flow at the funicular level, and whether these events occur simultaneously or appear before fetal stress or severe hypoxia.

Our group has previously detected differences between normal and pathological placentas in terms of vascular density and blood flow ^[13] but it was difficult to compare the images because they were limited to a particular area.

In the present study, we standardized the VPB to obtain reproducible measurements, and evaluated the results in normal and gestational diabetic pregnancies from the diagnostic and prognostic point of view.

2 Material and methods

We wished to determine the placental haemodynamic differences between normal pregnancies (NP) and gestational diabetes pregnancies (GDP) with good perinatal outcome, leaving aside those cases with adverse outcomes for a second group of study and possible publication.

We obtained 473 measurements in 43 NP, as control group (20 weeks-40 weeks of gestation) and compared these with 122 measurements obtained in 70 insulin-dependent GDP (22 weeks-40 weeks of gestation) studied every two weeks (see Table 1).

In 65% of all cases, the patients were referred to our center from other peripheral centers and gestational ages varied considerably at the time of inclusion in the study. We therefore selected and grouped NP from week 20 and GDP from week 22 (see Table 1).

Table 1. Distribution of the 3D-US measurements

Week gestation	20	22	24	26	28	30	32	34	36	38	40	Total pregnancies
NP(n)	43	43	43	43	43	43	43	43	43	43	43	473(43)
GD(n)	0	1	0	2	3	14	14	23	29	32	4	122(70)

Note. NP: normal pregnancy, GDP: gestational diabetes pregnancy

In the inclusion criteria for the present study, in the GDP group, all deliveries occurred at term (week 40 ± 6 days) based on normal maternal physiological and metabolic evolution and on fetal biophysical profile.

In both NP and GDP groups, there were no signs of loss of fetal wellbeing, and this was an absolute exclusion criterion for the present study.

Table 2. Rate age/parity in GDP group mean age: 30.7 +/- 2.6 (N = 70)

Age	N	Prim	Second	Third	Fourth
22	26	22	4	0	0
26	19	14	5	0	0
29	15	14	1	0	0
33	6	6	0	0	0
36	3	3	0	0	0
37	1	1	0	0	0

Maternal age was very similar in the both groups. In the GDP group, maternal age ranged from 22 years to 37 years (30.7 ± 2.6) (see Table 2), versus 18 years to 41 years (30 ± 3.8) in the NP group (see Table 3). No differences were recorded between fetal genders.

Table 3. Rate age/parity in NP group mean age: 30 ± 3.8 (N = 43)

Age/Years	N	Prim	Second	Third	Fourth
18	3	3	0	0	0
24	9	7	2	0	0
29	12	7	4	1	0
32	7	5	2	0	0
38	8	3	2	3	0
41	4	1	2	0	1

We recorded three successive volumes of the vascular tree in three consecutive measurements by 3D-US using 3-9 MHz multifrequency probe ultrasound (Voluson 730 Expert, G.E, Milwaukee, WI, USA). Images were analyzed in terms of blood FI, the number of vessels per volume of study or VI and VFI. Measurements were performed in a spherical volume of interest between the chorionic and basal plates.

In the analysis of the placental vascular tree, we used 3D-US PD with a pulse repetition frequency (PFR) of 600 Hz and a wall filter of 50 Hz at the level of greatest placental thickness. Placental thickness was measured from the chorionic plate to the basal plate, preferably at the point of umbilical cord insertion (although this was not an essential condition).

To assure reproducibility, the following standardized items were taken into account: 1) The areas selected were those with the highest density of vessels. 2) The viewing angle was not greater than 35° . 3) Absence of maternal and/or fetal movement. 4) Mean reading time was not greater than 10 seconds. 5) Three volumes were obtained per reading per patient. 6) All data were stored for later analysis and study. 7) All patient measurements were standardized two hours after meals and the last insulin injection in GDP cases.

VPB volumes were stored and analyzed off-line using Virtual Organ Computer-Aided analysis (VOCAL) ^[14-18] program integrated in the Voluson 730E and 4D view program. The conditions were standardized as follows: multiplanar mode and establishment of the work image in plane A, with the virtual axis of reference lying between the basal plate and the chorionic plate. Plates containing large-diameter vessels were excluded. Data were acquired automatically in a rotating sphere located on the virtual axis (see Figure 1).

The following biophysical patterns were automatically analyzed with VOCAL: FI or average color value of all color voxels (mean Intensity of Flow), VI or number of color voxels per volume of study (in %), and VFI or average color on the gray scale and sphere of study.

The Hadlock equation was used to estimate prenatal fetal weight ^[19].

The classic umbilical cord indices, pulsatility index (PI) and resistance index (RI) were evaluated and correlated with the placental 3D hemodynamic indices.

Results were expressed in three-dimensional hemodynamic indices values (VI, FI and VFI) for NP and GDP; the values were analyzed using the SPSS statistical program (now called PASW version 18). Student's *t*-test was used to analyze data distribution and F-score was used for analysis of variance, together with the chi-square test. Linear correlation or dependencies were analyzed with the significant two tail correlations ($p < .01$) Pearson coefficient *r*; values of 0.4-0.5 were considered weak, 0.6-0.7 moderate, and strong when they reached 0.8 or greater. Cut off point was taken as the most significant statistical value.

3 Results

In the GDP group, only 17% required cesarean deliveries due to pelvic-cephalic disproportion and of these, 16% of the newborns were in the 90th weight percentile with a mean birth weight of $3,826 \pm 231$ g. Most presented good neonatal condition, although 11% developed minor and transitory hypoglycemia and hypocalcemia without pathological or statistical significance (see Table 4).

Table 4. Mean weight of newborns compared between NP and GDP groups. Rate of cesarean sections and most frequent newborn complications. (PCD-Pelvis-Cephalic Disproportion)

	NP	GDP
Mean Weight	3,139 +/- 219	3,826 +/- 231
C-sections	0	17% (PCD)
Complications	0	11% hypoglycemia and Hypocalcemia (mild)

The 3D-US PD index showed an interclass correlation (ICC) of 0.9. The variation coefficiente was lower than 10% for FI and greater than 20% for VI and VFI.

In the NP group, placental blood flow showed a stable and progressive increase to reach a rough plateau, and decreased in the last weeks of pregnancy (see Figure 2). FI was the most stable placental hemodynamic index in all physiological pregnancies studied. Mean FI was 33 ± 3 before week 30, after which it increased to a 40 ± 6 , with the highest value at week 38. The results of statistical analysis of NP are shown in Table 5, with two highly significant peaks at weeks 32 and 38.

Table 5. Student T-test of flow index

Weeks pregnancy	20	22	24	26	28	30	32	34	36	38
week 20										
week 22	5.413									
week 24	-4.175	-15.508								
week 26	-1.222	-7.587	4.559							
week 28	-5.528	-16.956	0.219	-4.394						
week 30	-4.145	-7.328	-1.395	-3.909	-1.652					
week 32	-22.324	-40.206	-36.324	-26.553	-22.522	-13.198				
week 34	-11.480	-27.916	-16.928	-13.195	-11.425	-4.876	19.174			
week 36	-11.493	-18.526	-17.562	-12.955	-10.483	-7.550	6.603	-7.773		
week 38	-21.037	-31.284	-30.935	-22.229	-21.193	-16.552	-12.051	-24.545	-30.065	
week 40	-11.464	-15.463	-13.024	-11.691	-11.248	-9.270	-2.795	-9.422	-7.274	5.270

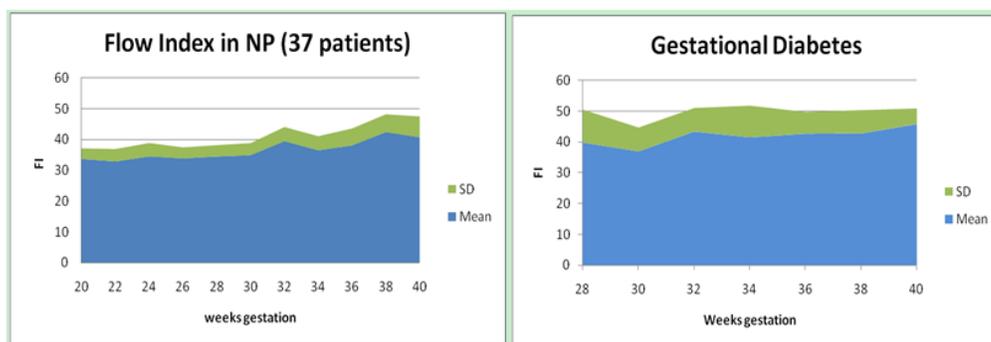


Figure 2. Placenta flow index (Mean FI values in blue, and standard deviation in green)

Gestational period showed a weak but significant linear correlation ($r = 0.5, p < .001$) that explained 23% of the variance with the formulae in Figure 3. There was also a weak but significant correlation with the estimated fetal weight ($r = 0.48, p < .001$), explaining 23% of the variance. In the whole series of NP, $FI > 45$ was found in 35 measurements (35/473 = 7.4%), all after 32 weeks of pregnancy. After week 32, $FI > 45$ became more common as the week of pregnancy increased (32 weeks, 5/37 = 14%; 34 weeks, 2/37 = 5.4%; 36 weeks, 6/37 = 16%; 38 weeks, 12/37 = 32.4%; 40 weeks, 10/37 = 27%).

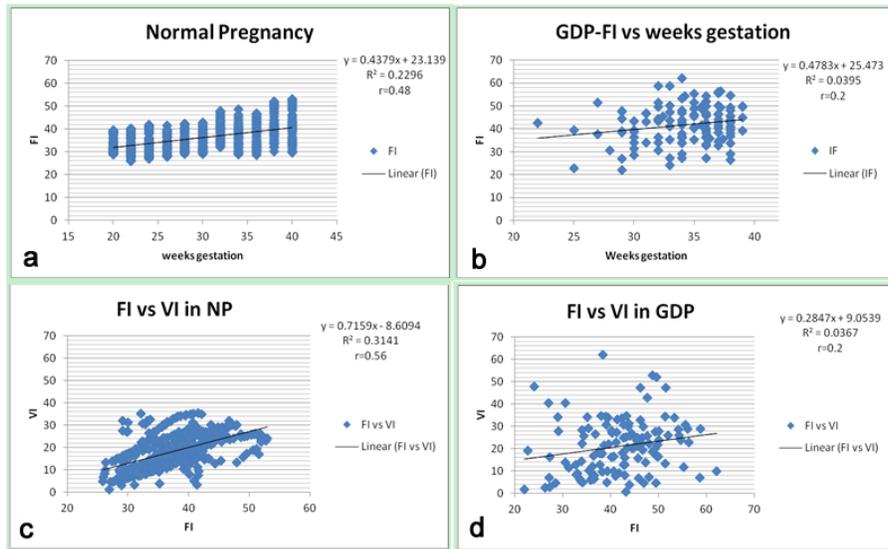


Figure 3. Correlation in NP and no correlation in GDP. Top, FI variations during weeks of pregnancy. Bottom, placental blood flow (FI) variations depending on vessel density (VI).

In umbilical cord PI and RI were each strongly correlated with both NP and GDP ($r = 0.7, p < .0001$), for the purpose of the present study we only used the parameter RI to express fetal circulation because it has a stronger correlation with FI, VI and VFI.

RI of the umbilical cord is highly correlated with the week of pregnancy (RI $r = -0.96$) to a lesser extent than the pulsatility index (PI $r = -0.98$) where 96% of variation depends on the gestational period. The correlation between PI and FI was $r = -0.44$ ($p < .0001$).

GDP showed significant difference in mean placental blood flow ($41.8 \pm 8.1, n = 122$) as well as variance ($F = 28.386, p < .0001$) compared with NP ($36.5 \pm 5.6, n = 407$): Student’s t -test of -6.72 and a $p < .0001$ with separated variances (see Figure 2).

Table 6. Student t -test of normal pregnancy (NP) versus gestational diabetes (GDP)

N Weeks	30	32	34	36	38	40	Total pregnancies
NP n cases	37	37	37	37	37	37	473
Mean \pm SD	34.9 \pm 3.9	39.4 \pm 4.7	36.5 \pm 4.6	38.1 \pm 5.5	42.4 \pm 5.9	40.7 \pm 6.8	(43)
GD n cases	14	14	23	29	37	4	122
Mean \pm SD	37 \pm 7.7	43.5 \pm 7.6	41.5 \pm 10.2	42.8 \pm 7	42.8 \pm 7.5	45.9 \pm 5	(70)
t -Test	ns	$t = -2.27, p < .02$	$t = -2.24, p < .03^*$	$t = -2.9, p < .005$	ns	ns	

* Significant differences in variance

The analysis of those differences depending on the gestational week (see Table 6) corroborated their higher values with the Student’s t -test, although some lost their significance due to their high variance.

Moreover, in 41/122 (34%) cases the FI was > 45 . The chi-square distribution at the cutoff point of 45 showed significant values of 57.3 ($p < .0001$).

Week of pregnancy (see Figure 3b) and foetal weight showed a weak correlation with FI ($r = 0.2$). Pulsatility and resistance index of the umbilical cord showed no correlation with FI.

For NP, regarding VI, Figure 4 shows that mean vessel density ($17.4 \pm 7.4\%$) formed a rough plateau before peaking at week 32. VI and FI (see Figure 4 bottom) correlated moderately and significantly ($r = 0.56$, $p < .001$) showing that the percentage of vessels per volume can explain approximately 31% of blood flow variability. Maximum VI occurred at week 30 ($25 \pm 7\%$).

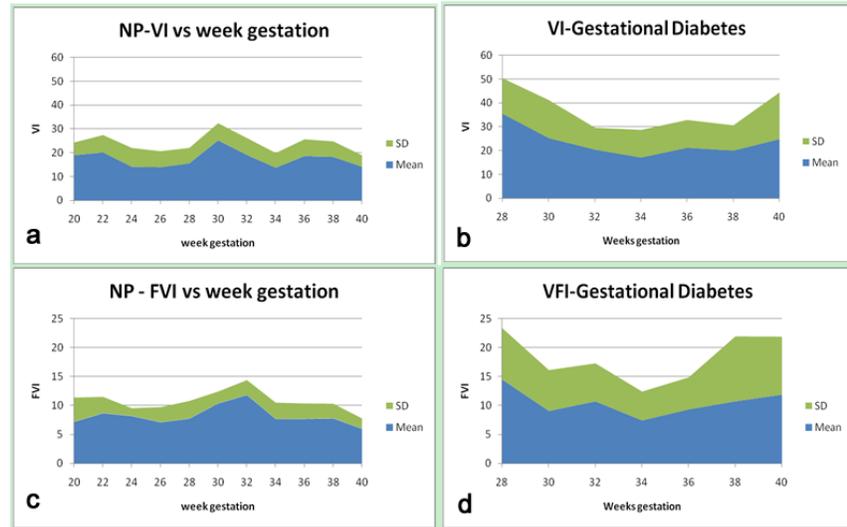


Figure 4. NP and GDP during weeks of pregnancy. In blue the mean values and in green the standard deviation. Top, placental vascular density (VI). Bottom, NP with a VFI of 8.2 ± 3 flow per vessel and GDP with 9.6 ± 7.7 blood flow per vessel.

No correlation was found between VI and week of pregnancy or fetal weight ($r = 0.06$).

In the whole series of NP, $VI > 31$ (the most significant cutoff) was present in only 9/473 measurements (2%).

For GDP, there was a trend toward higher values very early in gestation (see Figure 4) with significant differences in mean value ($20.96 \pm 12.2\%$) and variance ($F = 60.1$, $p < .0001$) compared with NP, and a Student's t -test of -2.5 , $p < .01$ with separated variances.

Values of $VI > 31$ were indicative of GDP (24/122, 20% of measurements) with a significant chi-square 21.5 and $p < .0001$, compared with normal pregnancies. All values of $VI > 36$ were recorded in GDP.

Intensity (FI) of blood flow was independent of the vessel density (VI) also known as percent of vessels per unit of volume as shown in Figure 4c.

For NP, regarding the Flow-Vascularisation Index (FVI), Figure 4c shows that mean FVI values (8.2 ± 3) form a rough plateau that is interrupted by a peak at week 32 (11.8 ± 2.6). FVI showed no correlation with week of gestation ($r = 0.22$), fetal weight ($r = 0.1$) or with PI and RI in umbilical cord ($r = 0.1$).

FVI is a composite parameter obtained from VI and FI; it had a weak correlation with FI ($r = 0.48$, $p < .0001$) and a strong correlation with VI ($r = 0.66$, $p < .0001$), as shown in Figure 5.

For GDP, VFI showed a marked trend toward higher values very early in pregnancy (see Figure 4d). Compared with NP, VFI of GDP placentas showed no differences in mean values (9.7 ± 7.7 , $n = 122$) but significant difference in variance ($F = 68.4$, $p < .0001$), with a Student's t -test of -1.7 and $p < .08$ with separated variances.

Correlation was weak with FI ($r = 0.4$, $p < .0001$) but moderate with VI ($r = 0.59$, $p < .0001$) (see Figure 5).

Values of VFI > 13 were indicative of GDP (31/122, 25% of cases); only 3.4% NP (16/473) had VFI > 13, with a significant chi-square of 54.3 and $p < .0001$. All values of VI > 14 were recorded in GDP.

Pulsatility and resistance indices of the umbilical cord showed no correlation with FVI.

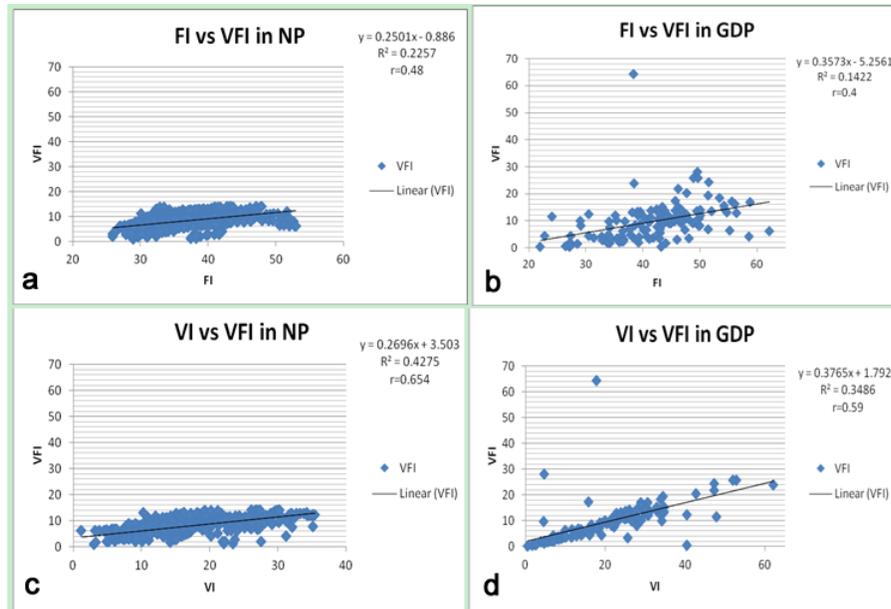


Figure 5. VFI correlated mainly with VI and to lesser extent with FI

4 Comments

In the present study, VPB technique tested in our measurements proved easy to standardize. From the point of view of standardization, the only difficulty was selecting the area of study in order to achieve reproducible results, but this was achieved by selecting the area of greater vascularization.

The results showed significant differences in the 3D placental hemodynamic indices of 43 NP compared with those of 70 insulin-dependent GDP that were followed from week 22 to the end of pregnancy. In NP, the blood flow (FI) proved a reliable parameter that varied according to the week of pregnancy (23%), VI (31%), and umbilical cord flow (RI, 20%) which suggests that FI could be linked to fetal development. FI progressively increased during NP, with two significant peaks: one week before delivery and at week 32. The latter may be related to the start of foetal organ circulation, in concordance with previously reported observations of hemodynamic visceral foetal development^[20].

In contrast, GDP showed continuously high FI values with a diagnostic cutoff point at 45, a value observed in only 7% of NPs and at the end of pregnancy. In GDP, mean FI showed a rough plateau with no correlation with fetal weight/gestational period ($r = 0.2$) or RI.

In NP, VI (number of vessels per volume expressed in percentage) was more variable than in GDP. VI was lower in NP ($17.4 \pm 7.4\%$) than in GDP ($21 \pm 12\%$) with a diagnostic cutoff point at 31%. Neither NP nor GDP showed a correlation between VI and fetal related parameters such as week of pregnancy, fetal weight or umbilical cord RI. For this reason, we consider that VI does not depend on fetal development and is therefore an indicator of the maternal component of the placenta. Moreover, VI normally peaked at week 30, two weeks before the fetal-related FI. Whether this indicates that changes appear in the placenta and in the umbilical cord prior to any change in normal fetal development is a matter of speculation, but deserves further study.

VFI showed a similar trend, with higher correlations in NP: correlation of VFI was weak with FI ($r = 0.5$) but high with VI ($r = 0.7$). In GDP, the correlation between VFI and FI was $r = 0.4$ and with VI it was ($r = 0.6$). This finding indicates that VFI is more similar to VI, in that it is not related to fetal development. Nevertheless, its peak appeared at week 32, coinciding with the FI peak, which we consider to be fetal-related.

As stated in the introduction, 3D studies do not enable separation of maternal and fetal circulation. Based on the results of the present study, it is rational to consider that the FI (which was lower) is more fetal-related, whereas VI showed higher variance. Our results demonstrated a weak but significant correlation between fetal weight and FI ($r = 0.4$, $p < .001$) whereas there was no correlation between fetal weight and VI. We found that maximum blood flow (FI) was related to the systolic pulse (RI) of the fetus (20% of its variance), while vessel density (VI) appeared to be related to the maternal lakes of the placenta where fetal vessels are too small to be detected. These findings indicate that anatomical and functional parameters justify the description of the technique as virtual placental biopsy; furthermore, they support its use for gestational evaluation at a distance, because standardized 3D capture provides virtual ultrasound images that can be processed remotely ^[21, 22].

In GDP, blood FI > 45 occurred in early pregnancy, in parallel with high vessel density (VI $> 30\%$). Despite this finding, FI and VI were weakly correlated, indicating that they measure a different aspect of circulation. In GDP, the so-called normal baby is influenced by the growth hormone-like effect of hyperinsulinism that develops in response to high maternal glucose levels. During this process, the Insulin-like somatomedine-C acts as a growth factor to increase foetal size ^[23-27], and the hemodynamic parameters FI and VI also increase, as demonstrated in the present GDP series, although we found no direct linear correlation.

It is unclear whether hemodynamic events in GDP are simultaneous or occur before severe fetal metabolopathy; however, in NP, physiological peaks were apparent in the placental-related parameters (VI) two weeks before they were observed in the fetal-related parameters (FI).

Finally, in GDP, VFI correlated better with VI and showed a non-significant increase due to its high variance, with a cutoff point at 13-14, while in NP, parallel increase was observed in both.

The results showed that placental blood flow (FI) was related to fetal circulation since it increases in macrosomic fetuses, while the percentage of vessels per volume (VI) was related to maternal circulation and had a lower value depending on the diabetes degree. 3D-US PD indicated a diagnosis of GDP for FI > 45 and VI $> 30\%$.

Based on the present results, it would be useful to design a system capable of differentiating fetal from maternal circulation by 3D-US PD. Distinction of fetal chorionic vessels from maternal lakes would validate the technique of optical biopsy. Careful standardization of the studied region is necessary to achieve comparable results.

The present study describes the technique of virtual placental biopsy, establishes the requirements for reproducible measurements, and suggests future improvements. Clinical departments will now carry out morphological diagnoses based on noninvasive biopsy techniques.

Pathologists and obstetricians will need to update their knowledge to cooperate at a distance (telediagnosis) otherwise laboratories will be empty of classical surgical diagnostic contents and full of advanced subspecialties according to new technology and technological advances ^[28].

We can conclude that ultrasound diagnosis and especially 3D Ultrasound, including VOCAL program in 3D Power Doppler ^[18], produce high quality images comparable and sometimes better than optical microscopy and should be interpreted by a pathologist. This should be the Optical Biopsy section in pathology departments where optical biopsies are received in teleconsultation. Since VPB are taken by three-dimensional techniques, it is not feasible for obstetricians

always to be present, but their expertise is required to make an exact diagnosis in this case of the placental structure and other vascular networks.

Using 3D-US power Doppler, gestational diabetes pregnancies could be detected by their high blood flow (> 45) and high vessel density ($> 30\%$).

In normal pregnancies, variations in blood flow index correlated with fetal parameters, while the vascularization index (VI), probably, correlated with maternal placental lakes, and physiological peaks occurred in the placenta two weeks prior to detection in the fetus.

The lack of correlation between blood flow and vascularization indexes in the case of GDP suggests that fetal developmental changes are affected by changes in the maternal component of the placenta for umbilical cord PI and RI showed no correlation with VI.

Abbreviations

FI = Flow Index; VI = Vascularization Index; VFI = Vascularization Flow Index; NP = Normal Pregnancy; GDP = Gestational Diabetes Pregnancy; RI = Resistance Index; PI = Pulsatility Index; VPB = Virtual Placental Biopsy; 3D-US PD = Three Dimensional Ultrasound Power Doppler; 3D-US = Three Dimensional Ultrasound

Conflict of interests

The authors have no competing interests in relation to the contents of the study.

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