Placental Virtual Biopsy

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Abstract—The present study described the technique of PVB (placental virtual biopsy) and its future improvements, establishing the requirements for reproducible measurements and consider their extension to iPhone or hand-held US devices. From the data collected FI (Flow Index) was related with foetal circulation, while VI (Vascularization Index) was supposed to be maternal-related. The 3D-US Power Doppler had been diagnostic to detect GD with an increase in FI>45 and number of vessels (>30%). Whether VI changes could predict FI or fetal changes is a matter of discussion.

***Index Terms*—Virtual Biopsy, Placenta, 3D-US, Hand-held US.**

Abstract—El studio describe la tecnica de la Biopsia Virtual Placentaria (PVB) y sus mejoras, estableciendo los requerimientos para unas medidas reproducible. De los datos recogidos se comprueba que el FI (Indice de flujo) tiene relacion con los parametros fetales mientras que la VI (Indice de Vascularizacion) se relaciona con parametros placentarios maternos. Ambos detectan la Diabetes Gestacional.

***Index Terms*— Biopsia virtual, Placenta, US-3D, US mobiles.**

I. Introduction

HEMODYNAMIC measures by means of 3D ultrasound are highly reproducible and 3D Power Doppler angiography provides accurate assessment of all types of terminal vascularization. The possibility to study 3D flow in complex vascular networks let us to consider and improve the technique of placental virtual biopsy (PVB), or non-invasive three-dimensional in-vivo hemodynamic analysis of the placental tissue. It is a virtual biopsy because as already defined by one of us [5.], [6.], it is done in vivo, analyze the tissue at functional and anatomical level and it is non-invasive.

Advantage of using 3D Power Doppler angiography was because this technique automatically provides information on: Serial Volumes, Grey-scale Indexes and calculation indexes such as VI, FI, VFI, and allow to manually or automatically calculating those parameter in a spherical regions of interest creating a PVB outside of the Chorionic and Basal Plates.

Three fundamental questions must be considered during the study of the 3D hemodynamic flow of the placental vascular tree: a- Funicular hemodynamic events and its relationship with the placental blood flow. In other words: Does the same phenomena occur in both the cord and the placenta? b- How objective is to assess villous circulation, given that placental vascular structures are a mixture of maternal inter-villous and foetal villous space. To be exact, we evaluate the whole placenta vascular tree, meaning maternal and foetal circulation. And finally c. - What is the influence of inter-villous flow on total placental flow?

In the 3D-US map we cannot differentiate maternal and foetal circulation, therefore an essential item will be to determine whether the hemodynamic events that occur in the placenta correlated with blood flow at the funicular level, and if they are simultaneous or chronologically they occur before foetal stress or severe hypoxia.

One aspect was evident and confirmed by our group-BIBLIO- there were morphological differences between physiological and pathological placentas in both vascular density and three-dimensional flow. Furthermore, there were differences between 2D and 3D vascular images particularly because this procedure only evaluates a particular area requiring a careful and standardized selection of the region of interest to achieve comparable results.

In the present study we describe the technique of PVB as well as its future improvements, establishing the requirements for reproducible measurements, evaluating the results in normal and gestational diabetes from the diagnostic and prognostic point of view.

II. Material and Methods

A. Cases and measurements

The 43 normal pregnancies studied between 20 to 40 weeks every two weeks (473 measurements) were compared with 70 insulin- dependent gestational diabetes studied between 22 to 41 weeks of pregnancy (122 measurements). See **Table I**.

Week gestation	**20**	**22**	**24**	**26**	**28**	**30**
NP (n)	43	43	43	43	43	43
GD (n)	0	1	0	2	3	14

32	**34**	**36**	**38**	**40**	**TOTAL PREGANCIES**
43	43	43	43	43	473 (43)
14	23	29	32	4	122 (70)

Table I Distribution of the 3D-US measurements. Number of measurements distributed between weeks of gestation. Normal pregnancy (NP) measured regularly every two weeks. Gestational Diabetes (GD) measured at term prior delivery.

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B. Standardization of the PVB technique

In the 3D-US device VOLUSON 730-E (expert) G.E. Iberica (Madrid. Spain) we recorded three successive volumes of the vascular tree in three consecutive measurements. On those images we analyzed: the gray-scale index (GI), the intensity of blood flow or Flow Index (FI), the number of vessels per volume or Vascularization Index (VI) and the Vascularization-Flow relationship Index (VFI).

Measurements were done in a spherical volume between the chorionic and basal plates.

For the analysis of the placental vascular tree we used a 3D Power Doppler angiography PFR (pulse repetition frequency) equal to 600 Hz and a wall filter of 50 Hz at the level of higher placental thickness. Placental thickness was evaluated measuring from the chorionic plate to the basal plate, preferable at the umbilical cord insertion (although this is not an essential condition).

To assure reproducibility (see **FIGURE 1**) the following standardized items were taken into account: 1.- That selected area were the one with the highest density of vessels. 2. - That viewing angle were not greater than 35 degrees. 3. - Absence of maternal and/or foetal movement. 4. - Mean reading time not greater than 10 seconds. 5. - Obtain always two volumes per reading per patient. 6. - Post-processed the stored data for later analysis and study.

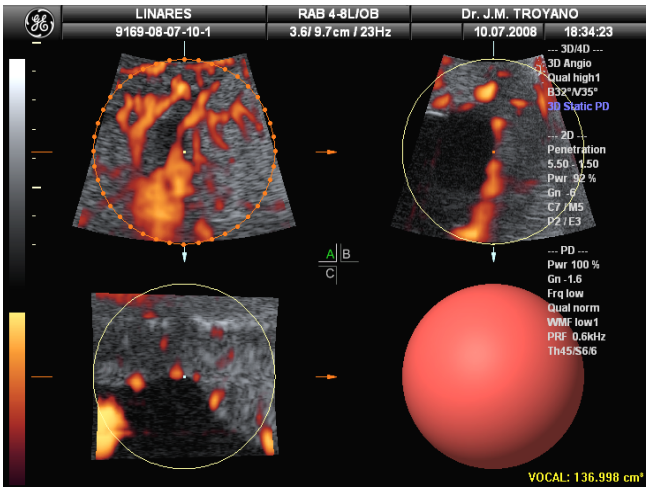

FIGURE 1 Flow multiplanar study of the PVB standardized in the present study. A. Transversal; B. Sagital; C. Coronal. The reference volume in cm3

C. Placental volume analysis

The volumes of the so-called PVB were stored and analyzed using **V**irtual **O**rgan **C**omputer-**A**ided ana**L**ysis (VOCAL) program under the following standardized conditions (Integrated in the Voluson 730E and 4Dview program for off line evaluation): In a Multiplanar Mode, establishing the work image in the plane A and having the Virtual Axis of reference lying between of the Basal Plate and the Chorionic Plate. Plates containing large calibre vessel were excluded. Data was acquired automatically in the rotating sphere located in the virtual axis (see **FIGURE 1**).

The biophysical patterns automatically analyzed with VOCAL were: GI or Gray-scale Values on the volume, FI or average colour value of all colour voxels (Mean Intensity of Flow), VI or number of colour voxels per volume of study, expressed in percentage, and VFI or Average Colour on the Gray scale and Sphere of Study

The 3D Doppler index showed an interclass correlation of 0.90.The coefficient of variation was less than 10% for GI and FI.

D. Foetal weight

The foetal weight was calculated prior pregnancy with Hadlock equation [1].

E. Funicular flow

The Classic Umbilical Cord indexes, namely pulsatility index (PI) in absolute values and Resistance Index were evaluated in order to correlate their flow with the placental hemodynamic indexes. IP and IR were highly correlated both in normal and gestational diabetes ($r=0.7$; $p<0.0001$), therefore were consider a one parameter expressing foetal circulation and for the study we choose RI because correlations with FI, VI and VFI were greater.

F. Statistical analysis

Results were expressed in Hemodynamic indexes (VI, FI and VFI) for the normal and insulin dependent gestational diabetes and were analyzed with the SPSS statistic program (now called PASW version 18). Parameters studied were: Data distribution analyzed with the Student t-test and F-score for analysis of variances, together with the Chi square test. Linear correlation or dependencies were analyzed with the coefficient or Pearson r, considering lower values of 0.4-0.5 in a significant two tail correlations ($p<0.01$).

III. RESULTS

The FI was the most stable placental hemodynamic index in physiological pregnancies studied every two weeks. As shown in **FIGURE 2** the initial 6 measurements were too variable, and therefore were considered errors linked to the training period of the volumetric technique, and excluded from the statistical evaluation.

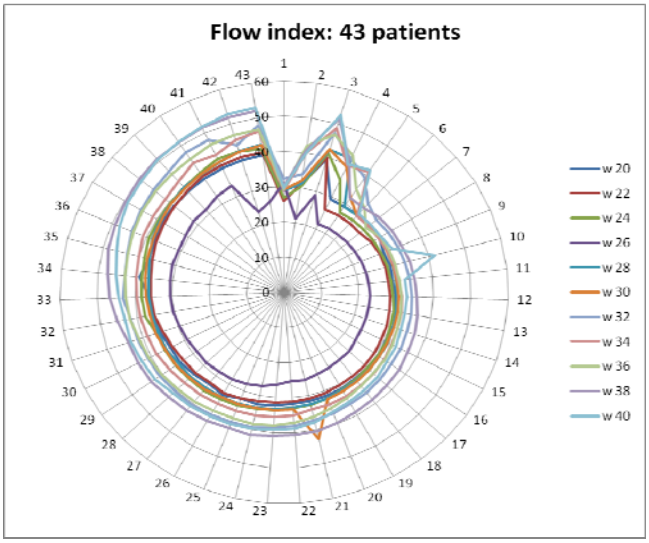

FIGURE 2A NP-Pool of 43 cases

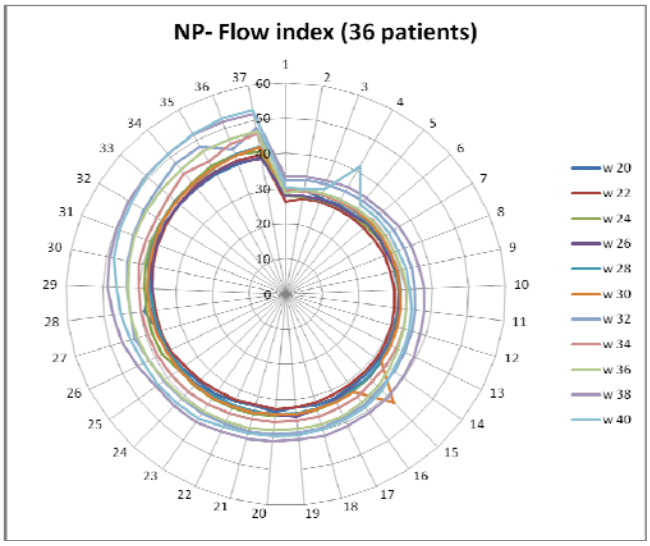

FIGURE 2B NP-Six first cases excluded

FIGURE 2 Flow Index in Normal pregnancies. Radians were the studied cases. On the left side the pooled cases including the six initial cases with greater variability that were considered an effect of training in the technique. On the left measurements excluding the initial 6 cases

A. Blood Flow Index (FI)

1) NP

They had a stable and progressively increase of placental blood flow to reach a plateau that decrease just at the end of pregnancy (see **FIGURE 2**). Before the 30 weeks of gestation, the mean FI was 33±3 increasing to a 40±6 thereafter, with the higher value at the 38 week. The statistical differences can be studied in **TABLE II**, with two highly significant peaks at 32 and 38 weeks.

The regression analysis with gestational period showed low but significant linear correlation (r=0.5 p<0.001) that explained 23% of the variance with the formulae in the **FIGURE 4**. There was also a low but significant correlation with fetal weight (r=0.48; p<0.001), explaining 23% of the variance (data not shown).

In the whole series of NP a FI>45 was present in 35 cases (35/473=7.4%), always after 32 weeks gestation. After that period, the number of pregnancies with a FI > 45 increased (32w, 5/37=14%; 34w, 2/37=5.4%; 36w, 6/37=16%; 38w, 12/37=32.4%; 40w, 10/37=27%).

The resistance index of the umbilical cord correlated with week gestation (RI r=-0.96) to less extend than pulsatility index (PI r= - 0.98) which 96% of variation depends on gestational period. Correlation of the IP with FI was r= -0.44.

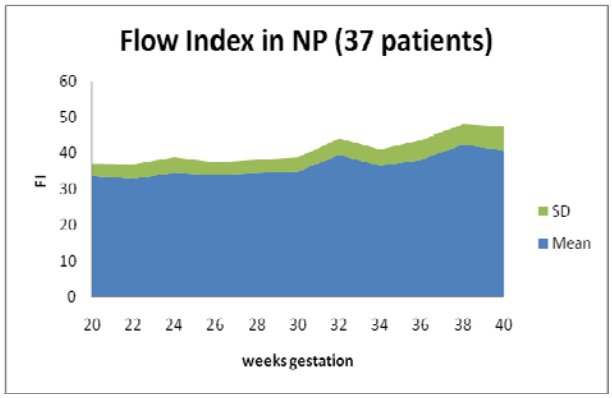

FIGURE 3A Normal pregnancy

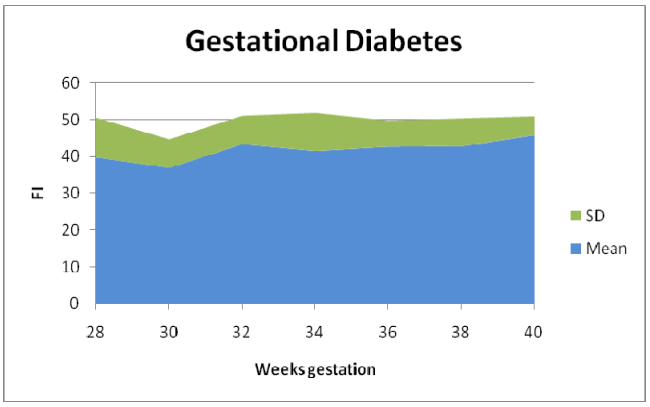

FIGURE 3B Gestational Diabetes

FIGURE 3 Placenta Flow Index. Mean FI values in blue, and standard deviation in green

Weeks pregnancy	20	22	24	26	28
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
week 34	-11.480	-27.916	-16.928	-13.195	-11.425
week 36	-11.493	-18.526	-17.562	-12.955	-10.483
week 38	-21.037	-31.284	-30.935	-22.229	-21.193
week 40	-11.464	-15.463	-13.024	-11.691	-11.248

Weeks pregnancy	30	32	34	36	38
week 20					
week 22					
week 24					
week 26					
week 28					
week 30					
week 32	-13.198				
week 34	-4.876	19.174			
week 36	-7.550	6.603	-7.773		
week 38	-16.552	-12.051	-24.545	-30.065	
week 40	-9.270	-2.795	-9.422	-7.274	5.270

TABLE II Student-t test values of the Blood Flow (FI) in normal pregnancies. p<0.0001. In green, differences with p<0.01 and in red, non significative differences. Progressive increase of blood flow during pregnancy, particularly in the third trimester (30-38w), that stops or decreases just before delivery (40w)

2) Gestational Diabetes

In GD placental blood flow showed significant differences in mean (41.8±8.1; n=122) and variance (F=28.386 p<0.0001) compared with NP (36.5±5.6 n=407) with a Student t-Test of -6.72 and a p<0.0001 with separated variances.

If we analyzed the differences at each gestational week (**TABLE III**) Student t-Test showed differences prior delivery, some not significant due to the higher variance (week 30).

Similarly in GD 41/122 (34%) cases showed a FI over 45. The Chi-square distribution at the cut point of 45 showed a significant Chi-square of 57.3 with a p<0.0001

Week gestation (**FIGURE 4B**) and foetal weight (data not shown) was not related with FI (r=0.2).

The pulsatility and resistance index of the umbilical cord had cero correlation with FI.

N Weeks	30	32	34
NP n cases	37	37	37
mean±SD	34.9±3.9	39.4±4.7	36.5±4.6
GD n cases	14	14	23
mean±SD	37±7.7	43.5±7.6	41.5±10.2
t-Test	ns	t=-2.27 p<0.02	t=-2.24 p<0.03*

36	38	40	TOTAL PREGANCIES
37	37	37	473
38.1±5.5	42.4±5.9	40.7±6.8	(43)
29	37	4	122
42.8±7	42.8±7.5	45.9±5	(70)
t=-2.9	ns	ns	
p<0.005			

TABLE III Student t-Test of Normal Pregnancy (NP) versus Gestational Diabetes (GD).* significant differences in variance

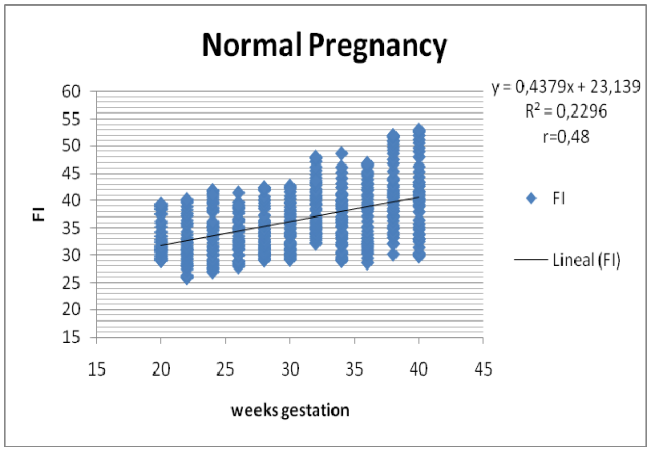

FIGURE 4A

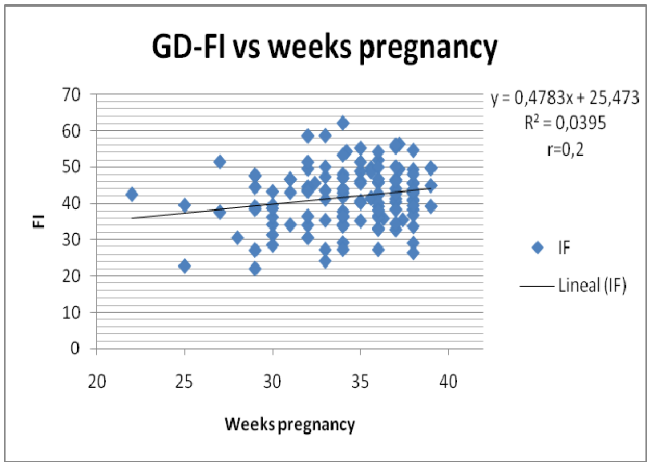

FIGURE 4B

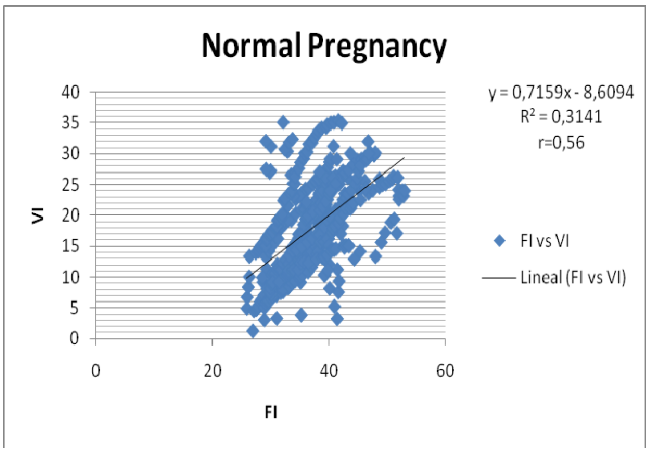

FIGURE 4C

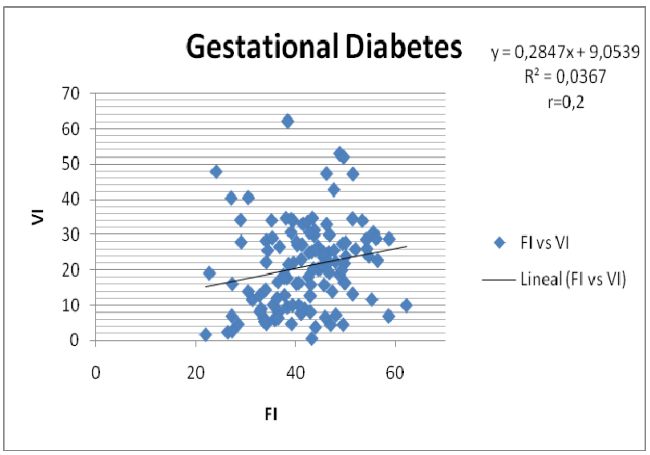

FIGURE 4D

FIGURE 4. Significant correlation in normal pregnancy versus no correlation in Gestational Diabetes. Top, variation of the FI according to week gestation. Bottom, the relationship between main placental flow (FI) and vessel density express in percentage (VI).

B. Vascularization Index (VI)

1) NP

FIGURE 5 showed the plateau of vessel density (17.4±7.4 %) broken by a peak in the 32 week of gestation. The VI and FI correlated (**FIGURE 4**) with a moderate and significant r=0.56 p<0.001 indicating that the percentage of vessels per volume explained around 31% of the blood flow variability. The maximum peak (25±7 %) is at 30 week gestation

No correlation was found with week gestation or foetal weight (data not shown) r= 0.06. Similarly, the PI and RI of the umbilical cord had zero correlation with the VI.

In the whole series of NP, the VI greater than 31 was present in only 9 /473 measurements (2%).

2) GD

There was a trend to have higher values very early (**FIGURE 5**) but vessel density of the GD placenta showed significant differences in mean (20.96±12.2 %) and variance (F= 60.1, p<0.0001) compared with NP, with a Student t-Test of -2.5 and a p<0.01 with separated variances.

Values of VI>31 were indicative of GD (24/122, 20% of cases) with a significant Chi square 21.5 and p<0.0001,

compared with normal pregnancies. Values of VI>36 were always GD.

Intensity of blood flow was independent of the vessel density or percent of vessels per unit of volume as shown in **FIGURE 4C**.

Week gestation, foetal weight, pulsatility and resistance index of the umbilical cord (data not shown) had a zero correlation with VI.

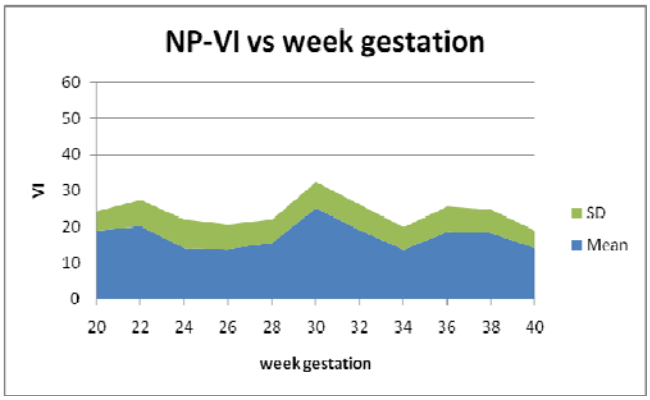

FIGURE 5A

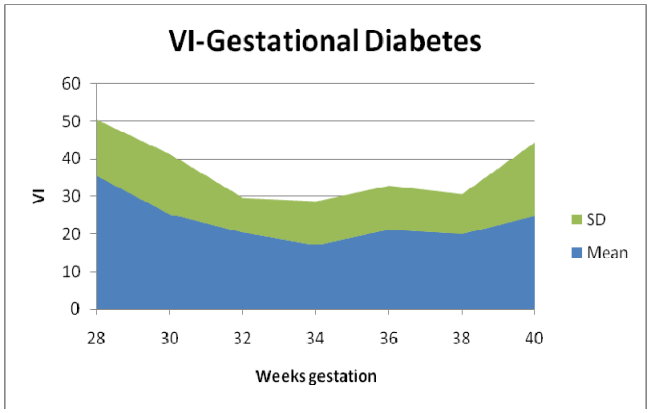

FIGURE 5B

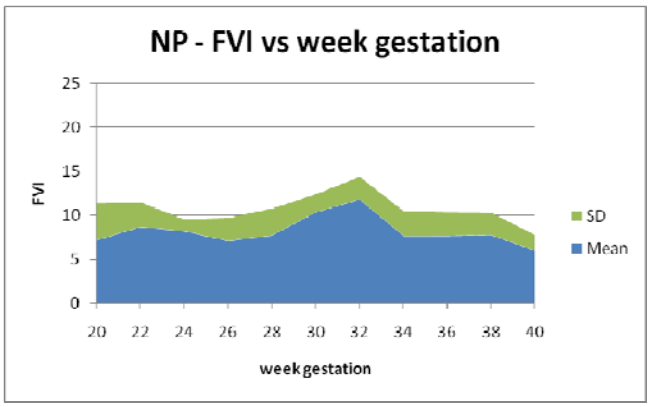

FIGURE 5C

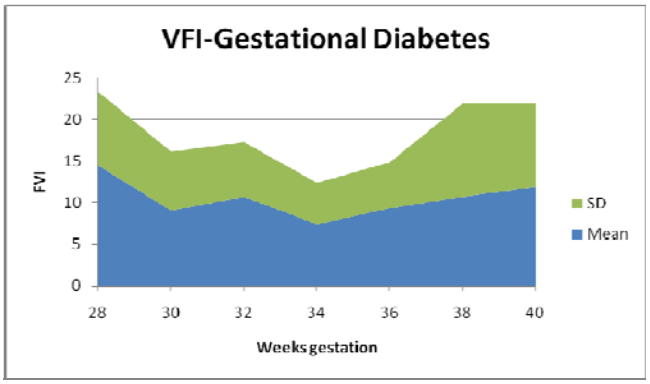

FIGURE 5D

FIGURE 5 Normal versus Gestational diabetes. Mean values in blue, and standard deviation in green. Top, the VI o vascular density express in percentage. Button relationship between Vascular-Flow index with a 8.2±3 flow per vessel in normal pregnancy and 9.6±7.7 in Gestational Diabetes.

C. Flow-Vascularization Index (FVI)

1) NP

FIGURE 5 showed the plateau of FVI (8.2±3) broken by a peak in the 32 week of gestation (11.8±2.6). Its correlation with week gestation (r=0.22) and with foetal weight (r=0.1) was inexistent, as well as with the PI and RI (r=0.1).

Being a composed parameter obtained from VI and FI its correlation was low with FI (r=0.48 p<0.0001) and a high with VI (r=0.66; p<0.0001) see **FIGURE 6**.

2) GD

It was a plateau value with a trend to have higher values very early (**FIGURE 5**), FVI of the GD placenta showed no differences in mean (9.7±7.7; n=122) but difference in variance (F= 68.4, p<0.0001) compared with NP, with a Student t-Test of -1.7 and a p<0.08 with separated variances.

Correlation with FI decrease (r=0.4; p<0.0001) and it was maintained moderated with VI (r=0.59; p<0.0001).

Values of VFI>13 were indicative of GD (31/122, 25% of cases) because there was present in only 3.4% normal pregnancies (16/473) with a significant Chi square 54.3 and p<0.0001. Values of VI>14 were always GD.

The pulsatility and resistance index of the umbilical cord had zero correlation with the FVI.

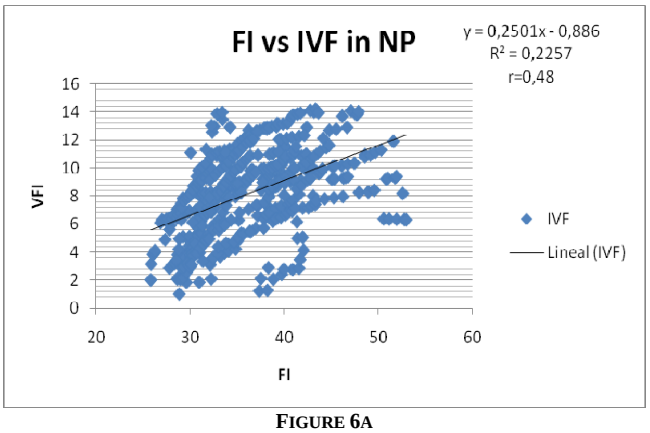

FIGURE 6A

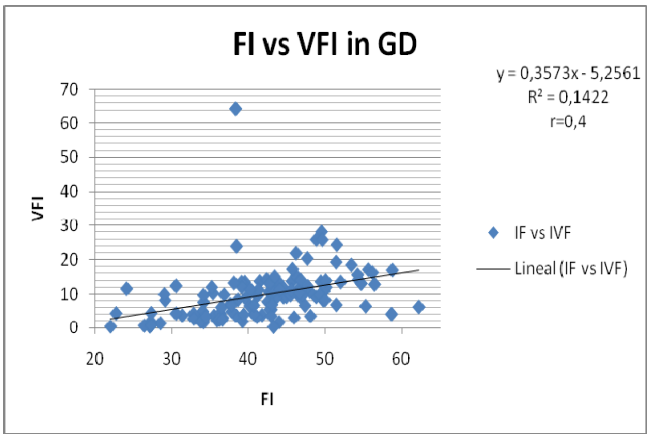

FIGURE 6B

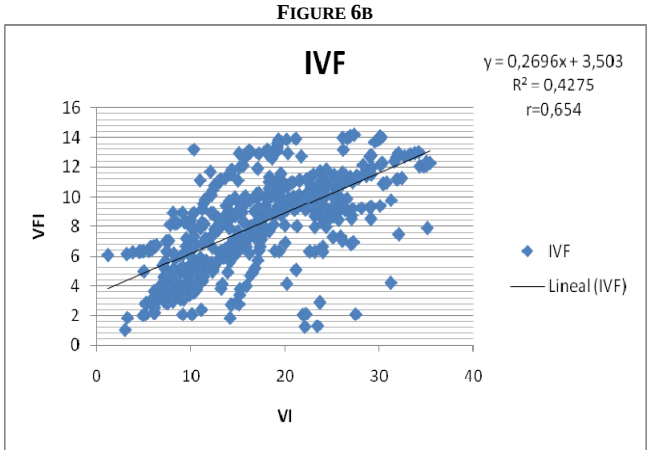

FIGURE 6C

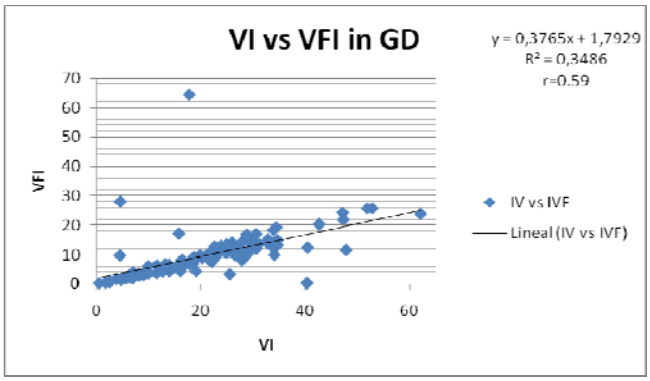

FIGURE 6D

FIGURE 6 VFI correlated mainly with VI and to lesser extend with FI

IV. DISCUSSION

The PVB technique tested in 595 measurements has been demonstrated easy to standardize and to reach a training plateau (10 cases were sufficient).

The 3D placental hemodynamic indexes of 43 physiological pregnancies followed from week 22 to the end of gestation compared with 70 insulin-dependent gestational diabetes showed significant findings. In normal pregnancies, the blood flow-**FI** was a very reliable parameter which variations were related with gestational period (23%), VI (31%) and umbilical cord flow (RI-20%). The FI progressively increase during pregnancy showing two significant peaks, one a week before delivery and another at week 32. The latter maybe related with foetal maturation and onset of foetal organ circulation [10]

In contrast, the GD showed a high FI from the start with a diagnostic cut point at 45, value achieved in 7% normal pregnancies but at the end of gestation. In GD the FI is a plateau with no correlation with foetal weight/gestational period (r=0.2) or RI. This could indicate that changes in GD were not linked with foetal development but with the maternal counterpart of the placenta.

In normal pregnancies, the **VI** or number of vessels per volume expressed in percentage was less stable/more variable, lower in NP (17.4±7.4%) than in GD (21±12%) that exhibited a diagnostic cut point at 31%. Both NP & GD showed no correlation with week gestation, foetal weight or resistance index of the umbilical cord; for that reason we considered it independent of foetal development. Moreover, normal peak at 30 week gestation was two week before the FI which is a foetal-related parameter. Whether this indicates that changes in placenta appeared before normal foetal maturation changes is a matter of speculation but should be further studied.

The **VFI** showed similar trend with higher correlations in NP. In NP correlation with FI was low(r=0.5) and it was high with VI (r=0.7). In GD the correlation with FI was r=0.4 and with VI was(r=0.6). This indicated that this parameter was almost identical to the VI that there was not related with foetal development. Nevertheless its peak was present at 32 week gestation as it was in FI considered by us as foetal-related.

As stated in the introduction maternal and foetal circulation could not be separated in 3D studies. As a result of our study, it is rational to consider that lower variance parameters, such as the FI, could be more foetal-related, whereas higher variance parameters, such as the VI, could be more maternal-related. The study demonstrated that there was a low but significant correlation between fetal weight and FI (r=0.4; p<0.001) whereas with VI was zero. We expected maximum blood flow (FI) to be related with the systolic pulse of the fetus (20% of its variance), while percentage of vessel density (VI) could be related with maternal lakes of the placenta where fetal vessels were small. These provided anatomical and functional parameters that justify to call it placental virtual biopsy-PVB .

In GD blood flow -FI > 45 was high early in pregnancy in parallel with a high vessel density (VI >30%). The study demonstrated that in spite of this trend both parameters were very low correlated measuring, therefore, different items. In GD the so-called normal baby is influenced by the growth-like hormone effect of the hiper-insulinism developed to fight against the high maternal glucose level. In this process the Insulin-like or C-Somatomedine acts as a growth factor increasing the foetal dimension, and therefore increasing hemodynamic parameters (IF & VI) as we demonstrated in the GD but not with direct linear correlation.

We do not know whether hemodynamic events in GD were chronological simultaneous or occurred before foetal stress or severe hypoxia, but in NP the physiological peaks appear two weeks before in the placental-related parameters (VI) than in the foetal-related parameters (FI).

Finally, the VFI better correlate with VI and showed a non-significant increase in GD due to its high variance with a cutting point at 13-14. This indicates that density of maternal lakes increased more than foetal tree in GD while in NP both growth in parallel.

Based of the results presented here, it would be of relevance to design a system capable of differentiating the foetal and maternal circulation by 2D Doppler- 3D US. At that point the criteria of optical biopsy[5][6] will be

achieved since we would be capable of evaluating foetal chorionic vessels from maternal lakes. With this technology we will be able to export this technique to the new appearing devices for US including hand-held ones as well as those probes functioning in mobile phones as specified in the previous chapter[11][12]

V. Conclusion

The present study described the technique of PVB and its future improvements, establishing the requirements for reproducible measurements. The 3D-US Power Doppler detected significantly GD by its high blood flow (>45) and high vessel density (>30%). Furthermore in NP variations in FI correlated with foetal parameters while VI correlated with maternal placenta lakes, being the physiological peak two weeks in advance in the placenta than in the foetus.

VI. References

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