

# Three-dimensional Power Doppler Ultrasound Study of the Placenta

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## ABSTRACT

Advanced ultrasound technology has been a valuable tool in the assessment of placental anatomy and physiology. Conventional two-dimensional (2D) sonography reveals placental morphological characteristics, 2D color Doppler can assess blood flow in the placenta, 2D power Doppler can evaluate placental vascular trees, and three-dimensional (3D) ultrasound gives more detailed information on the surface anatomy. Recent advances, such as 3D power Doppler with virtual organ computer aided-analysis (VOCAL) and histogram analysis can measure the placental volume, and assess uteroplacental and fetoplacental perfusions. In particular, 'placental vascular sonobiopsy' can specifically evaluate the second- and third-trimester placental blood flow and vascularity by obtaining several spherical samples from the placenta that will represent the entire placenta. This article presents normal placental development and pathological findings of the placenta using 3D power Doppler ultrasound, and discusses 3D power Doppler assessments of placental perfusion in high-risk pregnancies, such as fetal growth restriction, pregnancy-induced hypertension and preeclampsia, and, from this basis, re-establishes the importance of 3D power Doppler ultrasound as a screening, diagnostic, and surveillance tool in normal and abnormal pregnancies.

**Keywords:** 2D ultrasound, 2D color/power Doppler, HD-flow, 3D ultrasound, 3D power Doppler, Placenta, Placental vascular sonobiopsy.

**How to cite this article:** Tanaka H, Cajusay-Velasco S, Noguchi J, Hata T. Three-dimensional Power Doppler Ultrasound Study of the Placenta. Donald School J Ultrasound Obstet Gynecol 2014;8(4):400-409.

**Source of support:** Nil

**Conflict of interest:** None

## INTRODUCTION

The human placenta is one, or, if not, the most important structure in fetal growth and the maintenance of normal pregnancy. The establishment of its functions begins as

early as in the fourth week of pregnancy.<sup>1</sup> It acts as an endocrine organ, and transports and exchanges gases, nutrients, and wastes products for the fetus. It serves as a bridge that connects the mother and fetus. Impairment of this complex physiologic mechanism will result in an adverse pregnancy outcome. Hence, placental development has been a focus of research for decades.

Ultrasound evaluation of the placenta was started using conventional two-dimensional (2D) ultrasound. A sonographer evaluates its location, size, shape, and maturity using Granum's criteria.<sup>1</sup> However, these studies are limited because they only give information on the anatomy and not the functions.

To assess fetoplacental circulation, conventional 2D Doppler ultrasound was introduced. By identifying the blood flow in the umbilical artery, the pulsatility index (PI) and resistance index (RI) can be measured. The higher resistance and lower the blood flow, the more a pregnancy is at risk of complications.<sup>2</sup> However, circulation at low velocities of flow or in smaller vessels cannot be evaluated. Power Doppler ultrasound was introduced for assessment of the placental vasculature during the early 1980s. It detects the number of moving blood cells using the amplitude of the signals received from the vessels.<sup>3</sup>

In recent years, the use of three-dimensional (3D) ultrasound has been an adjunct to 2D ultrasound on morphological assessment of the surface of the human placenta. It uses state of the art programs, such as virtual organ computer-aided analysis (VOCAL) and extended imaging VOCAL (XI VOCAL) to measure the placental volume.<sup>3</sup> Studies showed that it gives more detailed information, specifically on visualizing the continuity and curvature of the placenta.<sup>4,5</sup>

With the evolution of ultrasound technology, power Doppler was combined with 3D ultrasound to yield more specific information on the placental anatomy and its function. This 3D power Doppler can be used to evaluate individual villous vascular trees and branches up to the tertiary stem vessels.<sup>5</sup> This ability to detect end-vessels is important in evaluating trophoblastic invasion, which is the key point in diagnosing high-risk pregnancies. Furthermore, 3D power Doppler ultrasound with histogram analysis can also assess placental perfusion by measuring these indexes: vascularization index (VI), flow index (FI), and vascularization flow index (VFI). The

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reproducibility of placental vascular indexes is significant in screening and monitoring pregnancies complicated with fetal growth restriction (FGR), pre-eclampsia (PE), and other placental pathological problems.<sup>5,6</sup>

## PLACENTAL VASCULATURE

The human placenta has two complex circulatory systems for blood: the uteroplacental and fetoplacental blood circulation. The uteroplacental blood flow starts with blood flow from the intervillous space to decidual spiral arteries. Early in pregnancy, the uterine artery shows extensive modification. The remodeling starts as the trophoblast differentiates into villous and extravillous trophoblasts. The villous trophoblast develops into chorionic villi where the transport of oxygen and nutrients takes place. The extravillous trophoblasts penetrate the maternal vasculature, and are further classified into interstitial and endovascular trophoblasts. The interstitial trophoblasts surround the spiral arteries at the decidua, while the endovascular trophoblasts penetrate the spiral arteries and are positioned in-between the endothelial cells. This replaces the endothelial lining and musculoelastic tissue of the vessel; hence, it is responsible for the 'high-flow and low-resistance' findings in Doppler ultrasound assessment of a normal uteroplacental circulation.<sup>7</sup>

On the other hand, the fetoplacental circulation starts from the umbilical cord, which consists of one vein and two arteries. As it enters the fetal surface of the placenta, known as the chorionic plate, the umbilical arteries branch to form the chorionic arteries. These are the stem arteries, which will further divide into branches. The first order branch or the primary stem villi is about 5 to 10 mm in length. The artery is about 1.5 mm in diameter with an

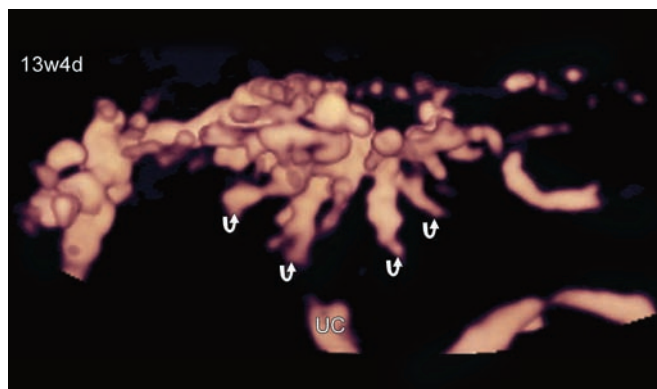
accompanying vein measuring 2 mm. The second order branch or the secondary stem villi will be the horizontal cotyledonary vessels which are about 1 mm in diameter. The third order villous branch or tertiary stem villi, once it curves toward the basal plate, will measure about 0.1 to 0.6 mm in diameter and 15 to 25 mm in length.<sup>7</sup>

## Normal Placenta

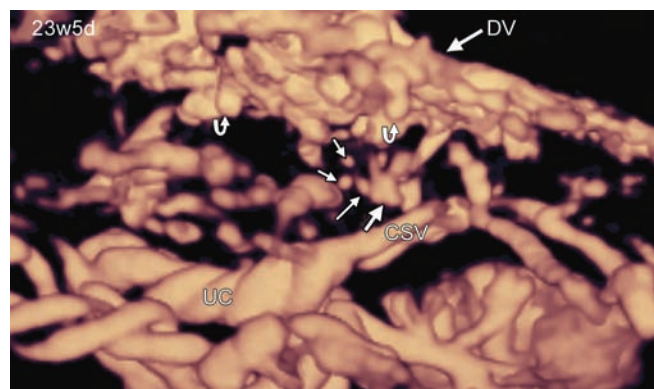
Assessment of the human placenta using 3D power Doppler gives us the opportunity to evaluate the villous vascular tree at different stages in relation to the age of gestation. At 13 weeks of gestation, the villous trees are about 200 to 400  $\mu$ m. The intermediate villi are developing with a few small mesenchymal branches (Fig. 1).<sup>5</sup> Fetoplacental capillary nets are present only in stems close to the chorionic plate. About one-third of the widened intervillous space (150-250  $\mu$ m in diameter) is occupied with fetal intravillous vessels.<sup>8,9</sup> Between 20 and 24 weeks, the villous trees continue to grow to more than 200  $\mu$ m. Mature, narrow villi and terminal villi develop. The intervillous space begins to shrink to about 60 to 150  $\mu$ m (Fig. 2).<sup>5,7,8</sup> At 32 weeks, placental vessels outgrow over the entire placental thickness, producing a tree-like appearance (Fig. 3).<sup>5</sup> The intervillous space continues to shrink. As pregnancy advances, villous trees continue to grow, and the intervillous space is no longer visible.<sup>8,9</sup>

## Jelly-like Placenta

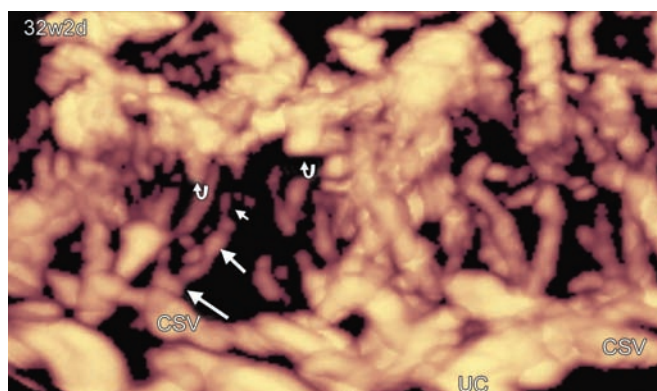
A jelly-like placenta depicted by 2D sonography is generally thickened, with a patchy decrease in echogenicity, and moves like jelly upon sudden abdominal movement or pressure.<sup>5</sup> This finding is usually a sign of impaired placental implantation that may give rise to an adverse pregnancy outcome.<sup>10</sup> 3D power Doppler shows



**Fig. 1:** 3D power Doppler ultrasound display of a normal placental vasculature at 13 weeks and 4 days of gestation. The ends of the spiral arteries (curved arrows) can be noted (UC: Umbilical cord) (Courtesy: Reprinted with permission from Hata T et al)<sup>5</sup>



**Fig. 2:** 3D power Doppler ultrasound display of a normal placental vasculature at 23 weeks and 5 days of gestation. The main stem vessels (large arrow), secondary stem vessels (median arrow), tertiary stem vessel (small arrows), and ends of spiral arteries (curved arrows) are clearly depicted (CSV: Chorionic surface vessel; UC: Umbilical cord) (Courtesy: Reprinted with permission from Hata T et al)<sup>5</sup>



**Fig. 3:** 3D power Doppler ultrasound display of a normal placenta at 32 weeks and 2 days of gestation. The main stem vessels (large arrow), secondary stem vessels (median arrow), tertiary stem vessel (small arrow) and ends of spiral arteries (curved arrows) are clearly shown (CSV: Chorionic surface vessel; UC: Umbilical cord) (Courtesy: Reprinted with permission from Hata T et al)<sup>5</sup>

a thick, heterogeneous placenta and reduced vascularity (Fig. 4).<sup>5</sup> Three-dimensional power Doppler ultrasound with glass-body rendering shows the impaired budding of villous circulation (Fig. 5).<sup>5</sup>

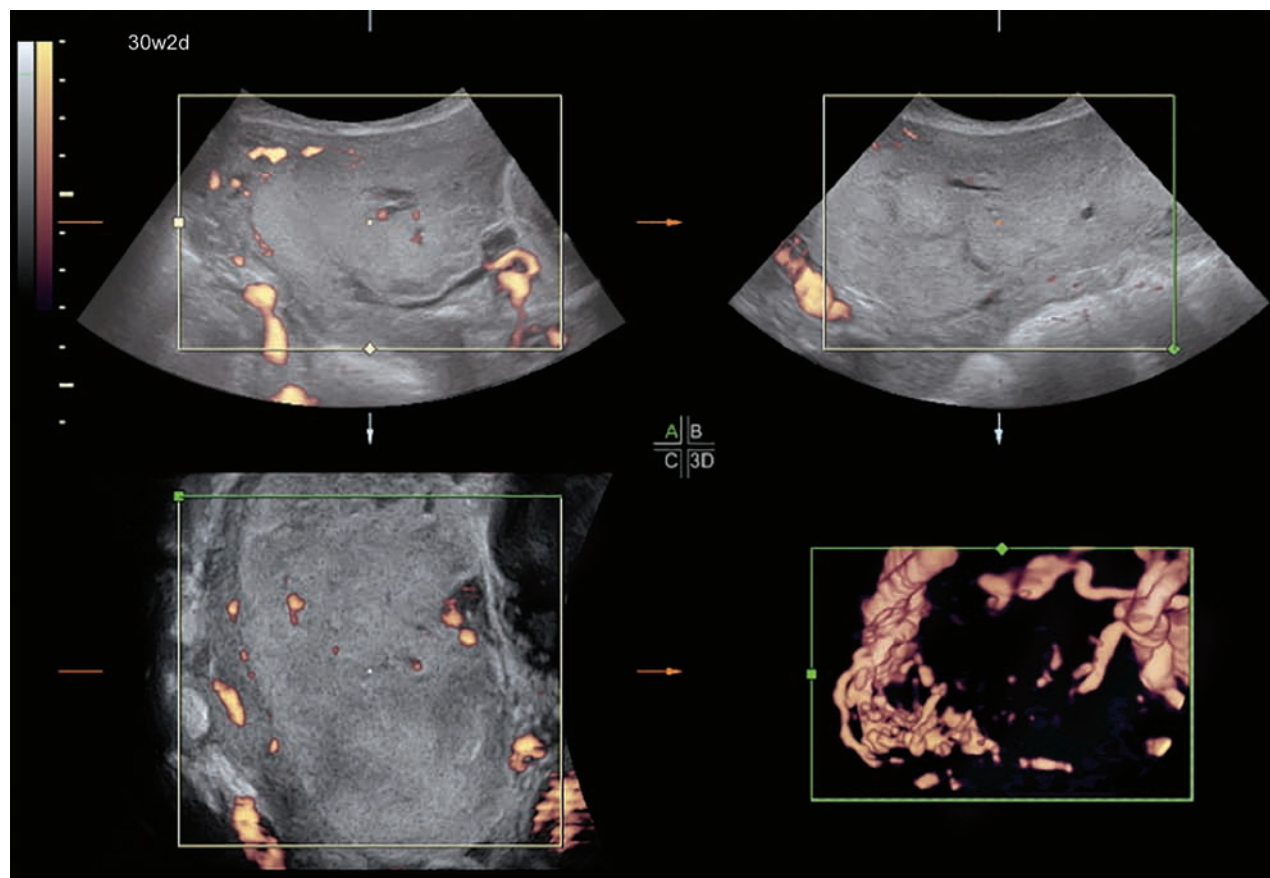
### Large Subchorionic Maternal Lake

Avillous spaces, or 'maternal lakes', are poorly reflective areas in the placenta which may give the placenta a multicystic appearance.<sup>11</sup> A subchorionic maternal lake

is a localized collection of blood or a hematoma arising from the rupture of chorionic vessels near the insertion of the cord.<sup>11</sup> 2D sonographic features are an oval-shaped cystic mass located on the fetal plate covered with a thin membrane (Fig. 6). Using 2D power Doppler or 2D HD-flow, there is an absence of blood flow (Figs 7A and B). 3D power Doppler clearly delineates the vascularity of the placenta and absence of flow in the affected area (Fig. 8). A gross specimen of the placenta shows the actual lesion (Fig. 9). Another similar pathological lesion is a subamniotic hematoma. Such lesions are associated with a risk of fetomaternal hemorrhage and FGR.

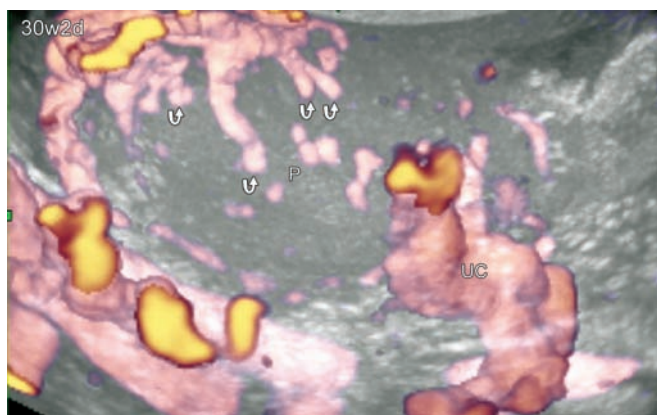
### Fibroma

About 60 to 78% of fibromas during pregnancy do not show a significant change in size. Only one-third may grow early in pregnancy.<sup>12</sup> Complications include abortion, preterm labor, placenta abruptio, malpresentation and postpartum hemorrhage. The location of a fibroma in relation to the placenta predisposes to the risk of postpartum hemorrhage, particularly the incidence of placenta accreta. Two-dimensional sonography shows the location of a fibroma just beneath the placenta, and 2D HD-flow shows its vascularity (Figs 10A and B).



**Fig. 4:** Multiplanar display of a 'jelly-like placenta' in a case of severe fetal growth restriction at 30 weeks and 2 days of gestation (Courtesy: Reprinted with permission from Hata T et al)<sup>5</sup>

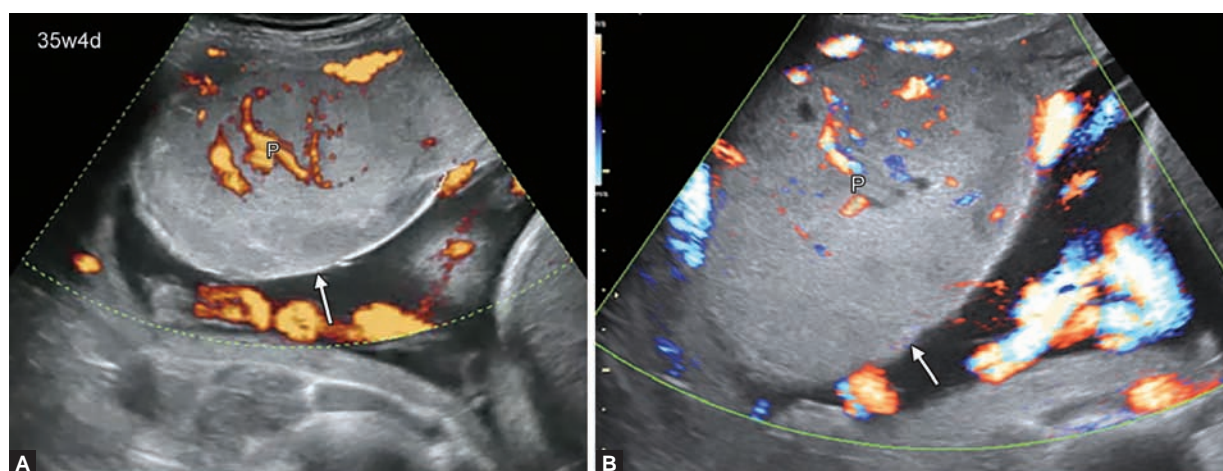




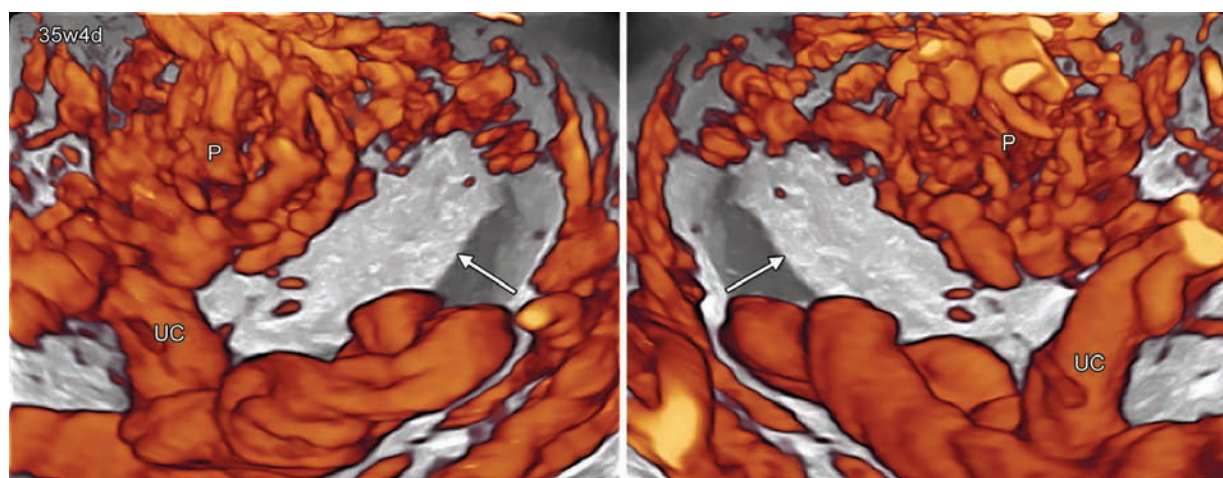
**Fig. 5:** Glass body 3D power Doppler ultrasound display of a jelly-like placenta (P) in a case of severe fetal growth restriction at 30 weeks and 2 days of gestation. There is a decreased placental vascularity, and the impaired budding of the villous circulation is clearly depicted. The ends of scanty spiral arteries (curved arrows) are shown (UC: Umbilical cord) (Courtesy: Reprinted with permission from Hata T et al)<sup>5</sup>



**Fig. 6:** 2D sonographic image of a large subchorionic maternal lake (arrow) in the placenta (P) at 35 weeks and 4 days of gestation. It is a cyst-like, echo-free space located near the umbilical cord insertion



**Figs 7A and B:** Large subchorionic maternal lake (arrows) of the placenta (P): (A) 2D power Doppler display showing the absence of blood flow and (B) 2D HD-flow display showing the absence of blood flow

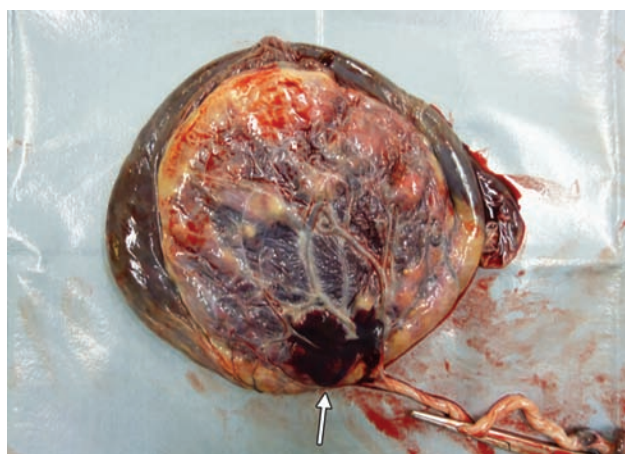


**Fig. 8:** 3D power Doppler ultrasound displays of a large subchorionic maternal lake (arrows) of the placenta at 35 weeks and 4 days of gestation. Absence of blood flow is evident (P: Placenta; UC: Umbilical cord)

Three-dimensional power Doppler clearly depicts smaller vessels that supply the fibroma, and the relationship between vessels and the placenta (Figs 11A and B). A previous study showed that there is a significant risk if

the placenta is implanted close to a fibroma compared with pregnancies in which there is no contact between the placenta and fibroma. The incidence was reported to be 60 vs 9% respectively.<sup>12</sup>





**Fig. 9:** Gross specimen of the placenta with a subchorionic maternal lake (arrow)

## Chorioangioma

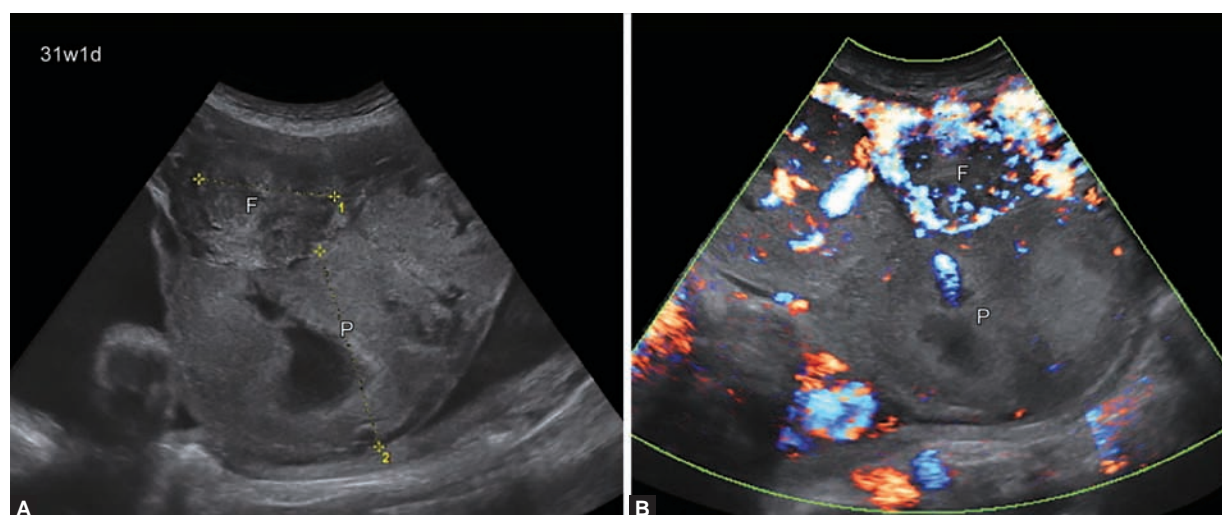
A hamartoma is when there is an abnormal proliferation of vessels arising from chorionic tissue.<sup>13</sup> A large chorioangioma may result in fetal cardiac overload because of

shunting of fetal blood to the tumor. This complication will lead to microangiopathic hemolytic anemia with fetal hydrops, polyhydramnios, premature labor and maternal and fetal coagulopathies.<sup>14</sup> 3D power Doppler depicts a 'highly vascularized placental mass including its feeding vessels and drainage at the fetal surface of the tumor' (Figs 12A and B).<sup>13</sup> The use of 3D power Doppler in this case is to monitor the tumor's hemodynamic status with advancing gestation.

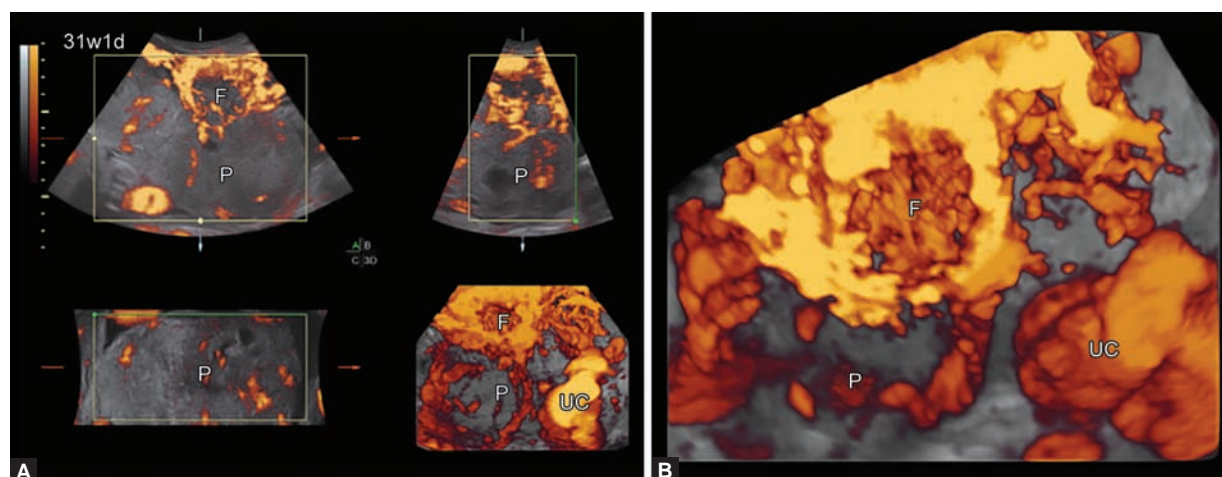
## 3D POWER DOPPLER ULTRASOUND EVALUATION OF PLACENTAL PERFUSION

### Placental Vascular Sonobiopsy

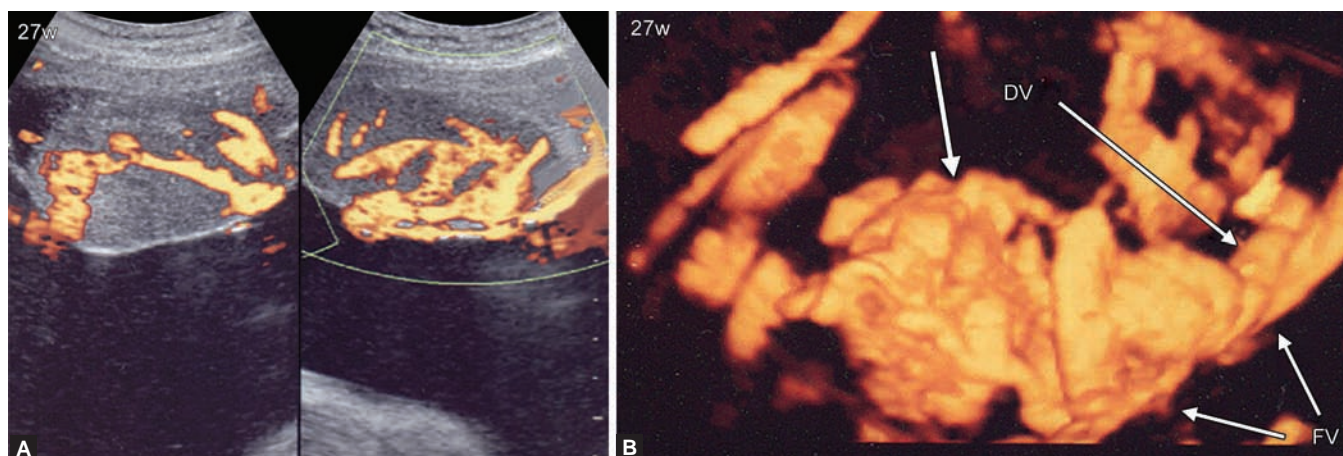
This technique was developed to evaluate the placental vasculature in the second and third trimesters.<sup>5,6</sup> Using 3D power Doppler ultrasound, a sample is taken to assess the thickness of the placenta, which will be a representation of the entire placental thickness (Fig. 13). It was initially performed by Merce et al<sup>15</sup> who took a



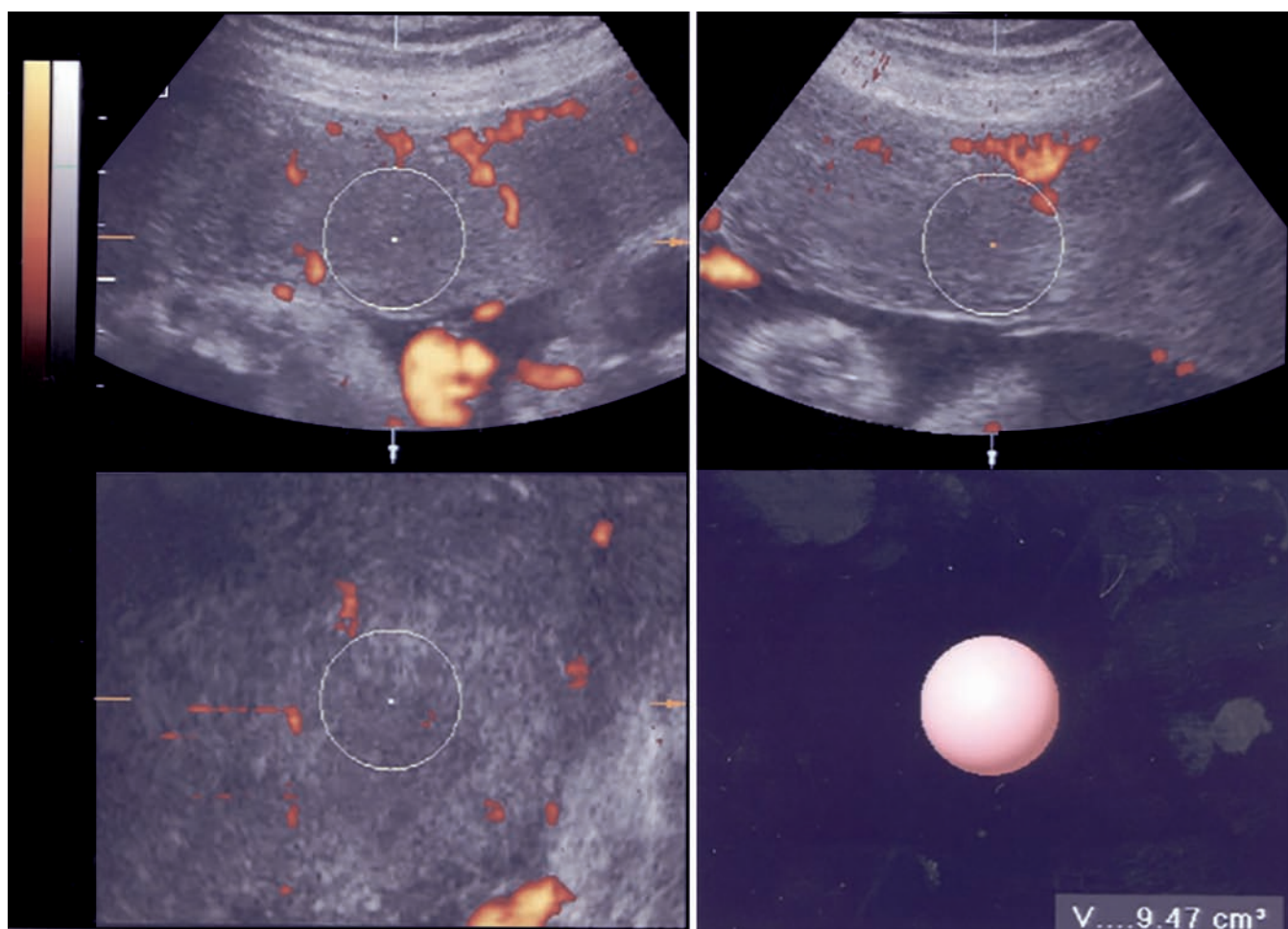
**Figs 10A and B:** Fibroma (F) just beneath the placenta (P) at 31 weeks and 1 day of gestation: (A) 2D sonographic image and (B) 2D HD-flow



**Figs 11A and B:** 3D power Doppler ultrasound display of a uterine fibroma (F) just beneath the placenta (P) at 31 weeks and 1 day of gestation: (A) multiplanar display and (B) 3D power Doppler image (UC: Umbilical cord)



**Figs 12A and B:** Chorioangioma (arrows) diagnosed at 27 weeks of gestation: (A) 2D power Doppler and (B) 3D power Doppler (DV: Drainage vessel; FV: Feeding vessel) (Courtesy: Reprinted with permission from Hata T et al)<sup>13</sup>

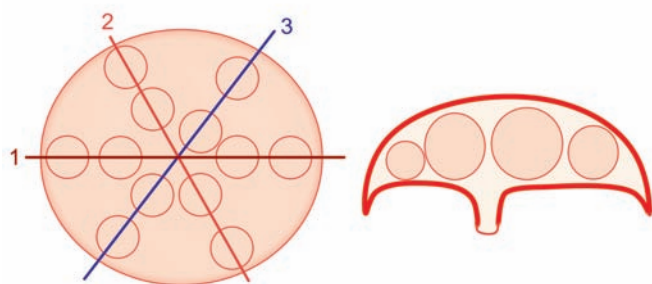


**Fig. 13:** Placental vascular sonobiopsy technique using 3D power Doppler ultrasound, where a sphere is taken as a sample from the basal to chorionic plate, representing the entire thickness of the placenta

sample from the basal to chorionic plate. Another study conducted by Martins et al<sup>16</sup> included four different areas in the placenta where samples could be taken, but the results showed that the most reliable area is a sphere taken between the basal to chorionic plate where vascularization is the most marked. Settings for the Doppler window must have at least a pulse repetition frequency of 600 Hz and wall filter of 50 Hz to achieve

maximal sensitivity.<sup>5,8</sup> With the procedure, three subsequent placental sections must be obtained with rotation of about 60° each, and then three to four spherical sampling sites are chosen in each plane (Fig. 14).<sup>5</sup> Then, using VOCAL histogram analysis, it calculates gray-scale and color values from the acquired sphere. Placental vascular indexes (VI, FI and VFI) were automatically computed (Fig. 15).



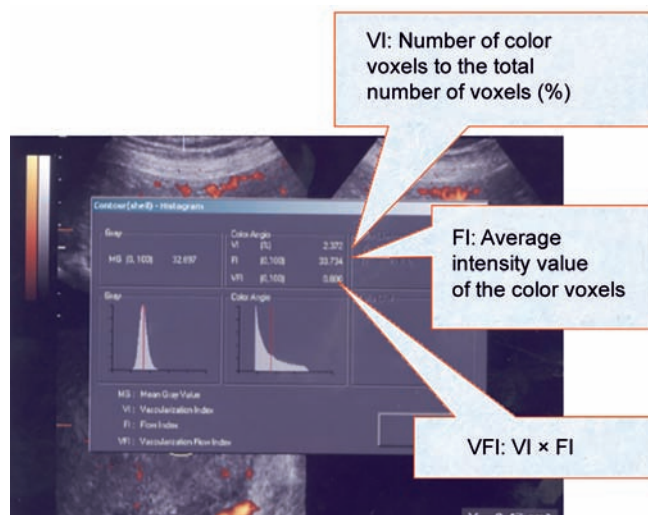


**Fig. 14:** Scheme of placental vascular sonobiopsy in the entire placenta (Courtesy: Reprinted with permission from Hata T et al)<sup>5</sup>

### 3D Power Doppler Indices of the Placenta

There are three indexes used to assess placental perfusion. VI is the proportion of the volume detecting a flow signal in the placenta or the presence of blood vessels. It is expressed as a percentage (0-100). FI is the mean flow signal intensity, and it is expressed in whole numbers (0-100). VFI measures the total vessels present and the intensity of flow by multiplying the VI and FI. It is also expressed in whole numbers (0-100).<sup>4,5</sup>

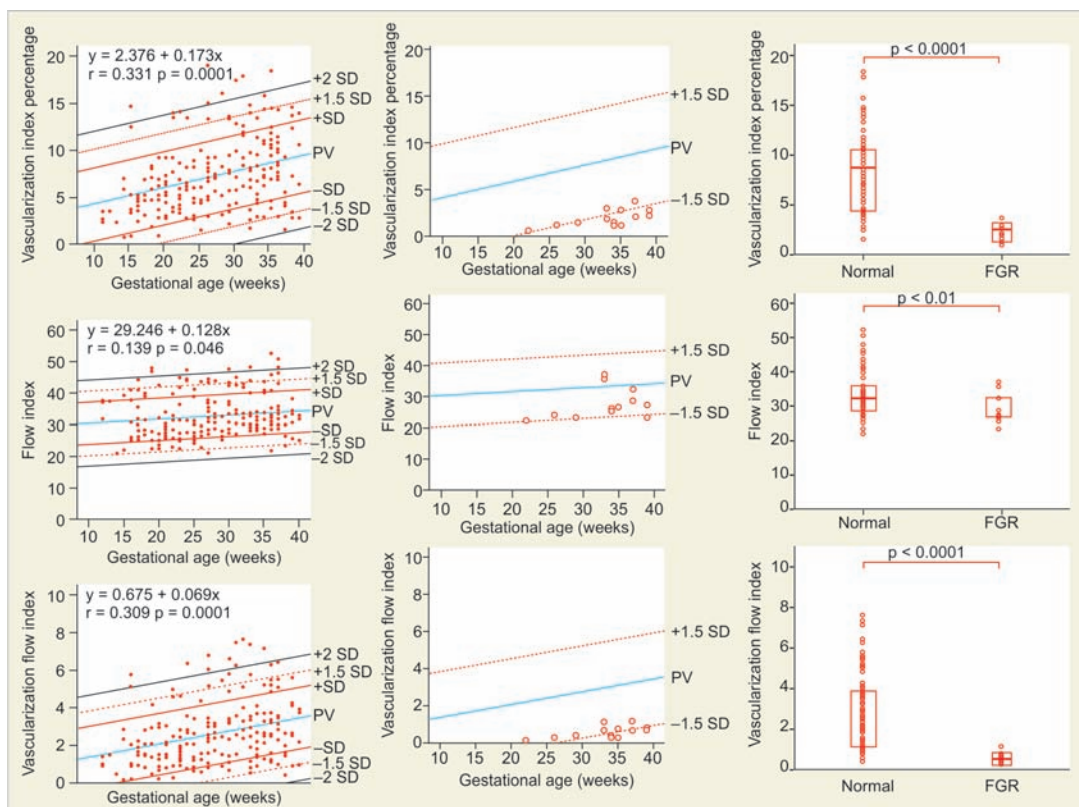
Noguchi et al<sup>6</sup> evaluated 3D power Doppler placental indexes in relation to the age of gestation. They plotted these indexes *vs* the gestational age, indexes of FGR in the reference ranges of the predicted value, and  $\pm 1.5$  SD, and compared normal and FGR pregnancies



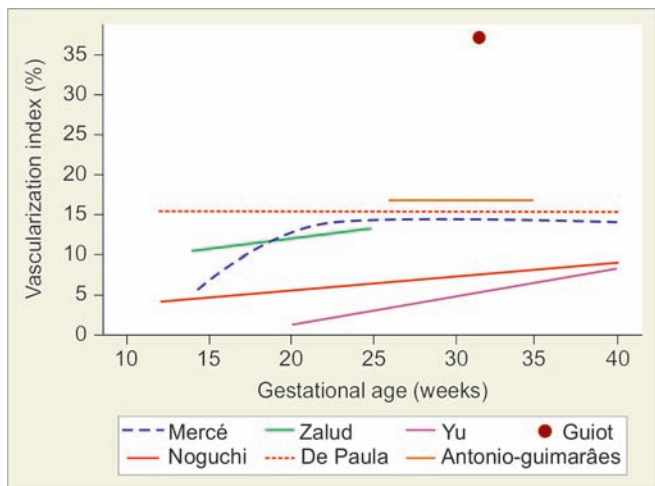
**Fig. 15:** The results of placental vascular sonobiopsy measurement of vascular indexes (VI, FI and VFI) are automatically displayed on the screen

(Fig. 16).<sup>6</sup> The results showed that all indexes had significant relationships with the gestational age in normal pregnancies. After 32 weeks of gestation, VI, FI and VFI values in FGR pregnancies were significantly lower compared to normal pregnancies respectively.

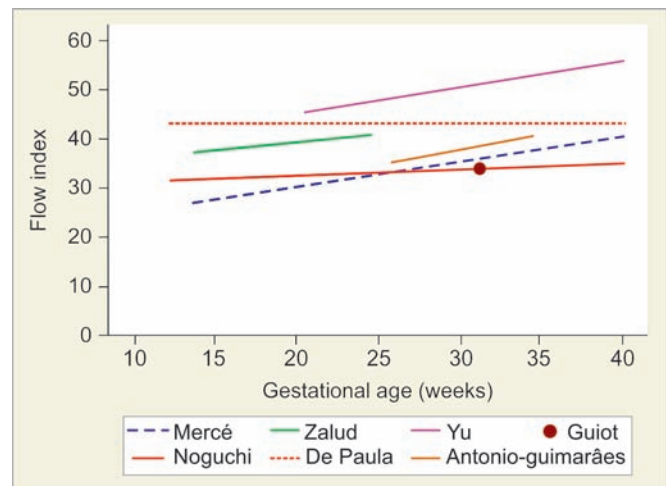
Hata et al<sup>5</sup> compared seven studies for the standardization of reference values for placental indexes (Graphs 1 to 3). They found marked differences in the predicted, mean, or median values among those studies.



**Fig. 16:** Placental vascular indexes in relation to the gestational age (left), placental vascular index values of fetal growth-restricted pregnancies with the predicted value and  $\pm 1.5$  SD (middle), and a comparison between normal and fetal growth-restricted pregnancies (right) (Courtesy: Reprinted with permission from Noguchi J et al)<sup>6</sup>



**Graph 1:** The vascularization index (VI) in relation to the gestational age in different studies (Courtesy: Reprinted with permission from Hata T et al)<sup>5</sup>



**Graph 2:** The flow index (FI) in relation to the gestational age in different studies (Courtesy: Reprinted with permission from Hata T et al)<sup>5</sup>

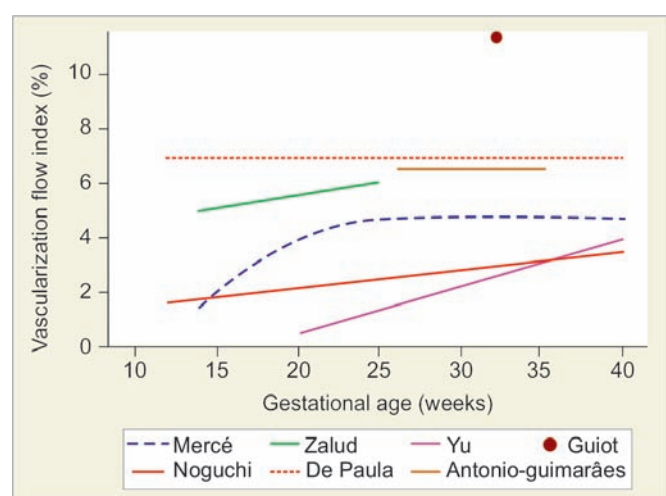
The possible factors leading to these differences are the process of acquiring a sample or sphere in the placenta, different machine settings, a different sample size and localization of the placenta.

### Prediction of Adverse Pregnancy Outcome

Inadequate trophoblast invasion or a deficit in branching of the terminal villi is the pathophysiology of FGR, PE, and intrauterine fetal death. Bleeding or hematoma within the placenta, fibroma that alters placental implantation, or chorioangioma that leads to fetal cardiac overload, are some of the causes of an adverse pregnancy outcome. In recent years, 3D power Doppler ultrasound has been the diagnostic modalities of choice for evaluating placental perfusion. Many studies have been conducted to improve the sensitivity of 3D power Doppler ultrasound for predicting an adverse pregnancy outcome.<sup>17-26</sup>

Hafner et al<sup>17</sup> measured placental vascularization indexes in the first trimester in a low-risk population to predict severe pregnancy risks. They compared data from normal, FGR, preterm delivery (<34 weeks), pregnancy-induced hypertension (PIH), all PE, severe PE, and severely problematic (a combination of complications) pregnancies. They compared the sensitivity of these indexes to other screening methods, such as the mean uterine artery Doppler at 12 to 24 weeks, and placental volume and PAPP-P measurement. The results showed that measuring 3D power Doppler placental indexes adds valuable information when evaluating those at risk. Vascular indexes are superior to biochemical markers, and give equal information on second-trimester uterine artery measurement.

Several studies have been conducted to measure 3D power Doppler placental indexes in patients with PE.



**Graph 3:** The vascularization flow index (VFI) in relation to the gestational age in different studies (Courtesy: Reprinted with permission from Hata T et al)<sup>5</sup>

They evaluated changes in the placental vascularization in PE, and found that all indexes and volumes are reduced in PE.<sup>18,19</sup>

In FGR pregnancies, Guiot et al<sup>20</sup> showed that FI is the most reliable indicator of severe placental insufficiency because of its low intraplacental variability. Naguchi et al<sup>6</sup> revealed that FGR after 32 weeks shows lower placental indexes. Lecarpentier et al<sup>21</sup> conducted an experimental study using a rabbit model by inducing FGR with NG-nitro-L-arginine (L-NAME). They found that measuring 3D power Doppler placental indexes is a sensitive way of detecting chronic hypoperfusion with very small placental vascularizations. They proposed the use of 3D power Doppler as a screening method in very early pregnancy.

Several studies also used 3D power Doppler to assess the placental function in cases of diabetes mellitus (DM).



Gonzalez et al<sup>22</sup> revealed that pregestational DM leads to an alteration in placental vascularity, and reduces indexes as early as in the first trimester compared to patients with no disease. However, there is no significant change in the placental volume in DM and control groups. In a study by Rizzo et al<sup>23</sup> in a group of patients with type 1 diabetic pregnancies, there was an increase in all placental indexes, and these indexes were even higher in patients with uncontrolled DM (HbA1c >7%). A similar study of pregnant women with DM was conducted by Jones et al<sup>24</sup> using a newer technique for data analysis. It was adapted from the Cavalieri principle of stereological analysis which involves random, systematic sampling to avoid bias. 'Each area of the placenta has an equal chance of being sampled, and that sampling should be done in a standardized manner'.<sup>23</sup> The fractional volume of power Doppler (Fr-Vol-PD) was calculated. The results revealed an increase in the fractional power Doppler signal at 12 to 18 weeks of gestation within healthy women and decrease in diabetic women between 12 and 20 weeks of gestation. This pilot study was promising, and encourages further investigation.

The common risk factors for placental insufficiency are an increasing maternal age and parity. Zalud et al<sup>25</sup> conducted a study, and revealed that these factors are associated with a reduced placental and uterine spiral vasculature volume and blood flow; hence, they are at risk of developing FGR, PE, aneuploidy, and other placental pathological conditions.

Due to advancing technology, there is an increasing number of women achieving pregnancy through oocyte donation either by *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI). This process subjects the mother to a semi-graft condition, and warrants surveillance of the developing fetus. Lopez et al<sup>26</sup> studied 33 mothers who achieved pregnancy after oocyte donation, and compared them to 42 mothers with spontaneous pregnancy. The results confirmed that placental perfusion was decreased in pregnancies from oocyte donation, and that spontaneous pregnancies have higher VI values.

## Reproducibility

An experimental study conducted *in vivo* by Morel et al<sup>27</sup> reported that the quantitative measurement of 3D power Doppler indexes was significantly correlated with true blood flow using a pregnant sheep model. Several studies reported the favorable reproducibility of measuring the 3D power Doppler placental volume and vascular indexes.<sup>5,28,29</sup> It also shows good intra- and interobserver agreements.<sup>6,30</sup> These results suggest that 3D power Doppler ultrasound can be reliably used in the assessment of the entire placenta and its perfusion.

Furthermore, it should be a good screening tool as early as in the first trimester to predict an adverse pregnancy outcome due to placental insufficiency. In advancing gestation, when viewing the entire placenta is not feasible, 'placental vascular sonobiopsy' is a favorable alternative to measure vascular indexes that represent the entire placenta.<sup>31</sup>

## CONCLUSION

The placenta and its vascularization comprise the most important organ for the maintenance of a normal pregnancy. Alterations in the development, such in the pathological cases presented, will lead to an adverse pregnancy outcome. Familiarization with a normal and abnormal anatomy and observation of the vascularization of the placenta using 3D power Doppler ultrasound are also important. The use of 3D power Doppler ultrasound in the assessment of morphology and placental perfusion was established in many studies as early as in the first trimester. In the second and third trimesters, where visualization of the entire placenta is difficult, 'placental vascular sonobiopsy' can be used when a sample is taken to represent the entire placental volume. 3D power Doppler can be a powerful screening, diagnostic, and surveillance tool in pregnancy complications due to placental insufficiency. The measurement of the placental volume and vascular indexes conducted in different studies shows a favorable correlation with the actual condition of the patient. Hence, clinicians can achieve early recognition and appropriate management.

## ACKNOWLEDGMENTS

The work reported in this paper was supported by a Grant-in-Aid for Scientific Research on Innovative Areas 'Constructive Developmental Science' (No. 24119004), and a Research Grant (No. 25462561) from The Ministry of Education, Culture, Sports, Science and Technology, Japan.

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