Aspects of placental morphogenesis and angiogenesis

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Abstract
Placental morphology and vascularization are important stages in the evolution of pregnancies. Placental morphogenesis and angiogenesis processes are studied by two-dimensional, three-dimensional and Doppler ultrasound. Ultrasound methods provide important data on the physiology and pathophysiology of fetal–placental exchange. The macroscopic and microscopic study of the placenta brings valuable information on the possible structural changes and implicitly allows assessing fetal-placental circulation. The ultrasound and microscopic evaluation of the placenta are complementary means of examination for the assessment of fetal–maternal exchange. These methods of investigation can be applied in the context of a strict knowledge of placental morphogenesis and angiogenesis.

Keywords: placenta, morphogenesis, angiogenesis.

Introduction
Placental vascularization represents an essential component in the normal evolution of pregnancy. Fetal–placental circulation disorders cause fetal hypoxia. This is why the assessment of placental circulation is a permanent concern of modern obstetrics [1]. Clinical and paraclinical investigation methods evaluate the development of the product of conception by assessing some parameters that result from the functionality of the feto–maternal-placental unit.

Ultrasound is a fundamental component of diagnosis in modern obstetrics, being one of the most important methods for the monitoring of pregnancy. Ultrasound is a non-invasive non-ionizing method, so that it can be used in the examination of pregnancy [2].

Two-dimensional, Doppler and, more recently, three-dimensional ultrasound provides a considerable amount of information on the physiological and pathophysiological aspects of feto–maternal-placental exchange.

Two-dimensional ultrasound brings guiding data on placental physiology (Figure 1).

Doppler examination has become an indispensable method, due to the information that it provides by the approach of vascular sites.

Combined three-dimensional and power Doppler ultrasound allows an accurate evaluation of placental vascularization. Three-dimensional ultrasound evidences the branches of placental vessels during one examination, allowing the characterization of normal or pathological vascular structures. Three-dimensional ultrasound in power Doppler mode provides useful information on the spatial distribution of the vascular network, in the case of the placenta the evidencing of arteries from third order stem villi [3].

Figure 1 – Two-dimensional ultrasound: aspect of the basal plate, chorionic plate and placental structure.

After delivery, the placenta can be studied macroscopically and microscopically.

The morphological exploration of the placenta is performed by qualitative methods (macroscopic and microscopic study) and quantitative methods (morphometric measurements). Technical progress over the past decades and the development of hardware and software technologies has opened new study perspectives for microscopic preparations [4].

The computer-assisted study is focused on modern morphometric methods that operate at pixel level and ensure a particular accuracy of the quantitative study method.
The main benefit of quantitative methods is the elimination of subjectivity from the interpretation of microscopic images [5].

Structural placental changes cause functional placental changes. In this context, morphometry represents an indirect non-invasive study method of placental physiology and pathophysiology [6].

Morphometric determinations undergo a continuous development and improvement process, being preferred because they eliminate subjectivity in visual perception due to the human factor, subjectivity is counteracted by the objectivity of the measurement process. In the case of digital image analysis, a computer that functions completely objectively, without the implication of the human factor performs the quantitative evaluation of information.

The ultrasound and microscopic evaluation of the placenta are necessary stages for the assessment of the evolution of pregnancy. These investigation methods will be applied in the context of a strict knowledge of placental morphology.

Placental morphogenesis and angiogenesis

The human placenta has a discoid, round or oval shape. The diameter of the placenta is 20–25 cm, and its weight at birth is approximately 500 g. The human placenta is a hemochorionic structure, in which the villous tree that contains fetal vascularization is surrounded by maternal blood.

In the process of placental formation, development and maturation, the essential role is played by the trophoblast, which ensures the nutrition of the embryo [7].

There are two stages in the development of the placenta: the previllous stage, between days 6–13 and the villous stage, from day 13 to delivery.

The previllous stage includes two periods: the prelacunar period – days 6–9 and the lacunar period – days 9–13.

In the prelacunar period, the trophoblast has two layers: a deep layer composed of clear cells, the cytotrophoblast, and a superficial layer represented by a dark cytoplasmic mass, without clear-cut cellular limits, the syncytiotrophoblast.

The cytotrophoblast or the Langhans’ cell layer consists of one row of cells, with basophilic cytoplasm. Mitoses are present in these cells [8].

This layer is initially continuous, and then it becomes discontinuous, with areas in which the syncytiotrophoblast comes into direct contact with the basal membrane. Starting with months 3–4 of pregnancy, the cytotrophoblast is reduced, finally disappearing towards the end of pregnancy. Isolated, rare, round or elongated cells, situated between the syncytiurn and the trophoblast basal membrane, may persist until the end of pregnancy – “residual Langhans’ cells”; they are situated in particular in the proximity of the capillaries.

The syncytiotrophoblast results from the fusion of the cytotrophoblast cells. This layer consists of a cytoplasmic mass with hyperchromic nuclei. During the first months of pregnancy, placentas contain nuclei that are relatively orderly arranged, while in near term placentas, the nuclei are also arranged as islets. The cell cytoplasm contains rough surfaced endoplasmic reticulum (rER) and smooth surfaced endoplasmic reticulum (sER), Golgi apparatus, mitochondria, as well as vesicles that play a role in the secretion and absorption processes. At the apical pole, the syncytiotrophoblast cells have microvilli. Sometimes, these can be evidenced with Hematoxylin–Eosin staining, as a “brush margin” [9]. The syncytiotrophoblast persists throughout the pregnancy. The cells of this layer have an intense secretory activity. The syncytial buds are the result of the bulging in the intervillous space of groups of nuclei along with the surrounding syncytioplast. These formations can detach, appearing free in the intervillous space. The fusion of several buds results in syncytial intervillous bridges, described by Langhans. Projections of the syncytioplast in the intervillous spaces, also called syncytial pseudopods, are found in particular in pathological placentas.

The “X”-cells are also called intermediate trophoblast cells; they have a trophoblastic origin. These cells are thought to secrete the placental lactogen hormone and the main basic protein. Electron microscopy shows numerous mitochondria with tubular crests in these cells. The cytoplasm of the “X”-cells is dark, with numerous vacuoles, and presents several nuclei. The “X”-cells play an important immunological role, in the synthesis of oncofibronectin [10].

Chorionic cysts occur in placental septa. These cysts are delimited by the “X”-cells and contain a fluid in which the secretion product of “X”-cells, the placental lactogen hormone, has been identified. The function of these cysts is not known, but their presence is not considered to be pathological [11]. “X”-cells in excess have been associated with an increased risk of pre-eclampsia and eclampsia.

In the lacunar period, the syncytiotrophoblast proliferates and determines the appearance of lacunae in the thickness of the basal decidua. These lacunae, initially small sized, gradually increase and merge. All lacunae will be lined by the trophoblast. On the other hand, the lytic activity of the syncytiotrophoblast results in the erosion of vascular walls (arteries and veins) and the penetration of maternal blood into the lacunae [12].

The villous stage includes two periods: the period of the elaboration of the placenta, from day 13 to the end of the fourth month, and the state period, in which the placenta is formed, from the fifth month to term. The formation of the definitive placenta (day 13–fourth month) involves the following changes: the formation of cotyledons and intercotyledonary septa; the progressive disappearance of the cytotrophoblast; the formation of syncytial buds. At the end of the fourth month, the placenta is completely formed. The placenta continues to develop by the growth of cotyledons and the development of the villous vascular system.

In the villous stage, the trophoblast situated in contact with the capsular decidua will be atrophied, due
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to deficient nutrition, and will be called chorion laeve. The trophoblast situated in contact with the basal decidua will progressively develop, will form placental villi and will be called chorion frondosum [13]. The period of elaboration of the placenta is characterized by the formation of villi. The following stages are distinguished:

**Formation of primary villi.** This stage starts as early as the lacunar period. Primary villi are completely formed between days 13–15. They consist of an axis represented by the cytotrophoblast, lined by the syncytiotrophoblast. These villi delimit the lacunae in which maternal blood is found. All these lacunae form the intervillus space. Maternal placental circulation is constituted.

**Formation of secondary villi.** It occurs between days 18–20. The extraembryonic mesenchyma penetrates into the axis of the villi, having a chorionic significance [14]. Secondary villi consist of an axis represented by the chorion, lined by the trophoblast, with the two layers, the cyto- and the syncytiotrophoblast. Secondary villi are also called chorionic villi.

**Formation of tertiary villi.** They appear starting with day 21, when hematopoietic islets and blood vessels are differentiated from the local villous mesenchyma. The connection of these villous vessels to embryonic circulation will result in the formation of fetal circulation [15] (Figure 2).

Figure 2 – Placental villi in various section planes (HE staining, ×200).

After they are formed, tertiary villi branch and generate daughter villi.

The branches of the villous tree differ depending on caliber, the aspect of stroma, the structure of blood vessels and location [16]. Part of these may have additional ramifications. All villous branches start from tertiary villi.

**Mesenchymal villi** are the precursors of the other types of villi. They appear in the first part of pregnancy. They are formed by an axis represented by the mesenchyma, covered by the trophoblast, with the two layers, the cytotrophoblast and syncytiotrophoblast. There are vascular structures in the connective axis. In the mesenchymal villi, the capillaries are poorly developed and do not have sinusoidal dilations. Between gestational weeks 5 and 7, these are the only vascularized villi. During the first gestational weeks, mesenchymal villi represent the proliferation area with the formation of villous branches. The differentiation of the other types of villi starts from mesenchymal villi. During gestational weeks 7–8, the mesenchymal villi become immature intermediate villi. The transformation of mesenchymal villi into immature intermediate villi continues until the end of the second trimester of pregnancy. As pregnancy advances, these villi are reduced, being replaced by the other types of villi. Small islets in the center of the villous tree may persist, which represent areas that will ensure the proliferation of new villous branches.

**Immature intermediate villi** appear in the first and second trimesters of pregnancy. These are villi with an increased caliber. The axis is represented by a reticular stroma, in which blood vessels and intercommunicating stromal channels occur. These channels allow the circulation of Hofbauer’s cells, considered to be fetal macrophages. However, these cells play many more roles. They are involved in the remodeling of the stromal connective tissue, as well as in the morphogenesis and angiogenesis of the villi. The immature intermediate villi ensure the rapid and effective growth of the villous tree. The first immature intermediate villi appear during gestational week 8. Between gestational weeks 14 and 20, these are the most numerous. The transformation of these immature intermediate villi into stem villi is initiated during the first trimester of pregnancy. The process will continue until term [17]. As a result, the number of intermediate villi decreases as pregnancy advances. Sometimes, they completely disappear near term, other times they persist as small areas in the center of the villous tree, serving as growth areas. The transformation of these immature intermediate villi into stem villi is progressive. Initially, stromal fibrosis occurs in the proximity of the vascular wall. An increase in the number of collagen fibers takes place, which will compress stromal channels, causing them to disappear. Immature intermediate villi represent the site of fetal-maternal exchange during the first two trimesters of pregnancy, when stem villi are not yet completely formed.

**Mature intermediate villi.** An important aspect in the understanding of the development of the villous tree occurs at the beginning of the last trimester of pregnancy. Then, the transformation of mesenchymal villi into immature intermediate villi is replaced by the formation of mature intermediate villi. This aspect is determined by angiogenesis, which starting with this moment no longer forms branches, the vessels only increasing in length. Mature intermediate villi are continued with terminal villi. It can be said that mature intermediate villi represent an intermediate development stage between mesenchymal and mature villi. Mature intermediate villi are long, thin, with peripheral branches. They have a zigzag trajectory. They generate terminal villi, representing a matrix for these structures. At the level of mature intermediate villi there are arterioles, collecting venules and numerous capillaries. These are structures that actively participate in fetal–maternal exchange, due to the increased degree of vascularization [18].

**Terminal villi** represent the final ramifications of
the villous tree, in the third trimester of pregnancy. They have an alveolar appearance, being compared to a grape grain. They are connected to the mature intermediate villi through a narrowed portion. During the third trimester of pregnancy, the villous maturation phenomena prevail over the villous tree growth processes. The formation of terminal villi is closely related to the increase in length of the capillaries, to the formation of capillary loops that will press the trophoblast and will form alveolar prominences in the intervillous space. Terminal villi are formed by the trophoblast and the connective axis in which there are peripheral capillaries with sinusoidal dilatations. The fusion of the basal capillary membrane with the trophoblast membrane results in the formation of a metabolic membrane, at the level of which fetal–maternal exchange takes place. This membrane is also called the vasculosyncytial membrane of terminal villi (Figure 3).

**Figure 3 – Vasculosyncytial membrane (HE staining, ×200).**

At the level of terminal villi, the degree of vascularization is increased, and the peripheral location of the capillaries makes these villi the main site of fetal–maternal exchange. The appearance of terminal villi can be considered because of the angiogenesis process. Deficient angiogenesis will decrease the number of terminal villi [19].

Finally, the chorionic plate and the placental tissue or the villous tree, around which maternal blood is found, forms the fetal component of the placenta.

The villous tree is formed by stem villi. The stem villi branches are represented by main stem villi, also called villous trunk. It represents the basal area of the villous tree, which ensures the connection to the chorionic plate. These villi generate four generations of branches, from first order to fourth order branches. These four generations are short, thick, detached from the trunk and situated in the proximity of the chorionic plate. Fourth order branches result in 2 to 30 (generally 10) unequal thinner dichotomizations, which are situated at the periphery of the villous tree. Part of these peripheral branches is divided and forms the so-called anchoring villi, which are connected to the basal decidua.

**Figure 4 – Artery of third order stem villus (HE staining, ×200).**

These vessels have three layers: intima, media and adventitia. The adventitia is continuous without a clear-cut delineation with the stromal connective tissue. There are extravascular myofibroblasts, parallel to the long axis of the villous tree. Their contraction and relaxation induce the regulation of the maternal blood flow in the intervillous space. Large caliber arteries and veins are surrounded by arterioles and venules. Their function is to stabilize the villous tree and implicitly, blood circulation. Considering the low degree of capillarization at this level, as well as the presence of degeneration phenomena in the trophoblast, these structures do not play a determining role in fetal–maternal exchange. Most of the peripheral branches of stem villi are continuous with mature intermediate villi. Arterioles and venules are found at this level, in which the endothelium is surrounded by 1–2 rows of smooth muscle fibers. Some venules do not have a muscle layer, the endothelium being surrounded by pericytes. These venules are called Rhodin’s collecting venules.

Paravascular capillaries have been evidenced in immature intermediate villi. They are connected to the arteries and veins by short vascular segments. They appear during the first stages of placental development and will not be evidenced in mature stem villi. These capillaries are considered to play a nutritive role, functioning as vasa vasorum.

Mature intermediate villi represent a junctional segment between the peripheral branches of the stem villi and terminal villi. In the mature intermediate villi, arterioles and venules are found. Large caliber vessels disappear from the distal half of mature intermediate villi. At this level, only capillaries with subtrophoblastic location will be found. Terminal capillaries form loops. There is no separation area between mature intermediate villi and terminal villi. The terminal villi contain capillaries with localized sinusoidal dilatations. The basal membrane of these villi is thin and composed of a single layer of trophoblast cells.
capillaries will form together with the trophoblast basal membrane, the vasculosyncytial membrane. In sinusoidal dilation areas, a local deacceleration of the blood flow occurs, which will favor fetal–maternal exchange [20] (Figure 5).

Concomitantly with the morphogenetic processes of the villous tree, vasculogenesis phenomena take place. The study of the development of the fetal–placental vascular system represents a complex aspect, permanently in the focus of attention of researchers [21].

Due to the special conditions under which the placenta develops, fetal-placental vasculogenesis and angiogenesis have a number of peculiarities.

At the level of placental villi, angiogenesis is dependent on oxygen and maternal blood nutrients. Fetal-placental vascular structures are permanently adapted to the needs of the product of conception.

As soon as the connection between placental and embryonic vascularization has been established, the placental vascular bed will undergo a continuous development process, in order to be able to meet the oxygen and nutrient requirements of the product of conception.

In any vascular bed, the increase in the blood flow is followed by changes in the morphology of vascular structures.

Doppler studies have evidenced that fetal vascular resistance decreases during pregnancies with a normal evolution and is altered in pregnancies with vascular pathology. The main modality to decrease vascular length and implicitly resistance is vascular branching. This branching can be achieved in two ways:

• formation of lateral branches;
• bifurcation or trifurcation of a main trunk.

Following this process, an increased number of vessels will result, which will have a parallel arrangement in section.

Angiogenesis can also be achieved by an increase in the length of the vessel, without branching, which will lead to an increase in vascular resistance. This occurs either by the proliferation of endothelial cells from the already existing vessels or the recruitment of new endothelial progenitors from the surrounding tissues [22–24].

Fetal–placental angiogenesis modulates the development of villi. In normal pregnancies, the growth of the capillaries is biphasic.

• in the first phase, an angiogenesis process occurs by branching, following which capillary loops will be formed;
• in the second phase, an increase in the length of vascular structures takes place without their branching.

It can be seen that the morphology of the villi follows the stages of angiogenesis.

In the first trimester, the villi are short and covered by abundant trophoblast. Inside these structures, there is a well-developed capillary network, arranged around a central vessel. Third trimester villi are covered by a thin trophoblast layer, they are long thin structures, with longer and denser vessels.

The development of placental vascularization depends on the presence of growth factors and receptors for these factors. A noteworthy aspect is that vessels at this level do not have vegetative innervations, flow resistance being controlled by vasoactive substances from the vascular bed microenvironment.

Fetal vascularization is created by the local de novo formation of the capillaries. The vasculogenesis process starts on day 21.

The first precursors of the endothelium are situated in the stroma of the villi and are called hemangioblasts. Because they already express markers of endothelial cells, they can be evidenced by the use of the QBend10 monoclonal antibody, which shows the presence of CD34 [18].

Hemangioblasts differ from their mesenchymal precursors by the absence of extensions. They are polygonal cells, with a seriate arrangement. Spaces between hemangioblasts are small, the cells being joined together by desmosomes and tight junctions. The mesenchymal cells that surround them can send extensions that penetrate among these cells. The process described above is under the control of VEGF-A, which is responsible for the differentiation, growth and aggregation of hemangioblasts. This cytokine is present in large amounts in the first phases of angiogenesis. It is secreted by trophoblast cells and macrophages located in the stroma.

In the human placenta, the formation of tubular structures from hemangioblast cords starts on day 21. The appearance of capillary segments marks the transition from secondary to tertiary villi.

Starting with day 28, hemangioblasts form structures with well-defined lumens, with peripheral endothelial cells. The mesenchymal cells that surround them will subsequently become pericytes and will contribute to the reserve of endothelial cells required for the modeling of the capillary bed during pregnancy. Pericytes, along with endothelial cells, will start to synthesize the basal membrane. This will completely surround the capillaries in week 10.

An extremely important aspect is the fact that the presence of hematopoietic cells is seen in a capillary network that is not yet connected to the embryonic vascular structures. The connection between embryonic and placental vascular structures will be

Figure 5 – Capillary stasis (HE staining, ×200).
established subsequently, by means of allantoids vessels. Starting with day 32 until the end of the first trimester, the structures resulting through vasculogenesis will be transformed into capillary networks by the interaction between two parallel mechanisms:

- elongation of existing structures through angiogenesis, without their branching;
- their branching, either by the formation of lateral extensions or bifurcation.

In small mesenchymal villi, angiogenesis occurs without branching and the capillary network formed is small sized. During the evolution of pregnancy, as the villi caliber increases (immature intermediate villi), branching angiogenesis results in the development of an important capillary network, the capillaries being situated at the periphery of the mesenchymal axis.

During the first stages, angiogenesis is controlled by VGFA (vascular endothelial growth factor A) and its two receptors VEGFR-1 and VEGFR-2, their expression gradually decreasing during the course of pregnancy. In contrast, as pregnancy advances, an increase in the expression of PI GF is seen, which stimulates angiogenesis by the increase in the length of the existing capillaries [25–27].

In the third week of pregnancy, some of the capillaries located in the center of immature intermediate villi will grow. In several weeks, a media and an adventitia will develop around them, which are formed by a process of concentric fibrosis of precursors that express desmin, alpha and gamma sm-actin, as well as mesenchymal markers such as vimentin. These will be subsequently followed by the expression of sm-myosin. Arteries and veins will be subsequently formed.

The formation and maintenance of the structure of these vessels is under the control of two angiogenic factors: angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2) and of their receptor Tie-2. Genetic studies have demonstrated that Tie-2 deficiency is associated with a poorly developed capillary network [28].

In the second part of pregnancy, the fibrosis process at the level of stem villi progresses radially towards the trophoblast. Involved in this fibrosis process, the capillary network progressively diminishes, as central vessels turn into arteries and veins. At term, only a few capillaries at the periphery of stem villi are found. The mechanism by which the capillaries regress is not known. It should be noted that the regression of the capillaries occurs at the same time with the diminution of the trophoblast and the disappearance of macrophages, both cell populations being known as sources of VEGF-A.

While in the stem villi a regression of the capillary network occurs, in the distal structures of the villous tree, a new capillary network is formed. In this way, as they develop, the villi adapt their structure, the capillary network, the exchanges between fetal and maternal blood occurring in the distal portion, while the proximal portion contains vessels with a role of conducting blood to the product of conception.

From week 25 to term, the development pattern of the capillaries changes from angiogenesis in which vessels are formed by branching to angiogenesis in which the capillaries predominantly increase in length. This process will determine a change in the morphology of the villi and the appearance of new types such as mature intermediate villi.

The analysis of markers at this development stage shows a decrease in trophoblast proliferation and an increase in endothelial proliferation throughout the length of capillary structures, which will result in their elongation [29].

The final length of the capillaries will exceed the increase in length of the villi, which is why the capillaries will have a sinuous trajectory inside the axis and a peripheral location, right below the extremely thin trophoblast layer. In this way, an extremely thin vasculosyncytial barrier is formed, which will favor the exchanges between fetal and maternal blood.

Another morphological peculiarity is that 5–10 peripheral capillary loops are interconnected by means of long capillaries situated in mature intermediate villi. In this way, fetal blood, before leaving the placenta, passes several times to the level of the vasculosyncytial barrier, thus favoring gas and nutrient exchanges between placental and fetal blood.

The correlation between growth factors and the development of villous architecture suggests that the balance between VEGF-A, PI GF and their receptors, determines the geometry of the villous vascular bed. Under the control of VEGF-A, angiogenesis will develop during the first two trimesters of pregnancy, which will result in the branching of the capillaries and the formation of a rich capillary network, with low blood flow resistance in mesenchymal and immature intermediate villi. In contrast, PI GF and its receptor VEGFR-1 will form in the last trimester of pregnancy a poorly developed capillary network, formed by long capillaries with high blood flow resistance [30].

The balance between the expression of VEGF-A and PI GF genes is at least partially under the control of partial oxygen pressure. The expression of VEGF-A and its receptor in placental tissues takes place in the presence of low partial oxygen pressure, while PI GF is expressed during the last period of pregnancy, when maternal blood flow considerably increases and with it, the oxygenation of placental tissues [31, 32].

Because of the mechanisms that control the development of the placenta, the villous vascular system has some peculiarities that are not found in any other locations.

In the first place, arteries and veins have a structure adapted to a low-pressure regime, presenting a thin tunica media. Vasa vasorum are absent from the adventitia, being replaced with the few vessels left after the regression of the peripheral capillary network in the stem villi. In the absence of high partial oxygen pressure, a sufficient oxygen uptake at the level of the vascular wall is provided from maternal blood [33].

Unlike other body tissues that have an extremely abundant capillary network, the vascular bed of the placenta is composed of a large number of long, little branched capillaries.
Correlations between the histological structure of the placenta and the ultrasound methods

The exact knowledge of placental morphogenesis and angiogenesis phenomena will allow establishing correlations between the histological structure of the placenta and the ultrasound methods used in the monitoring of pregnancies [34]. The development of Doppler techniques, which use ultrasound frequency variations, has allowed direct access to the functionality of the feto-maternal-placental unit [35] (Figure 6).

Figure 6 – Umbilical artery: normal PRI.

The abnormal aspect of velocimetric indices at the level of umbilical arteries is accompanied by an increase in the resistance of umbilical-placental circulation. The pathological basis of this phenomenon is represented by a process of reduction in the number of tertiary villi and arterioles.

The changes in Doppler velocimetry at the level of the umbilical artery reflect distal vascular pathology at the level of intraplacental circulation, but these Doppler ultrasound alterations become obvious at a late stage. It is considered that only when 60% of intraplacental circulation is obstructed, significant changes in the Doppler wave pattern are produced in the umbilical artery [36].

Color Doppler allows detecting intraplacental vascular flow [37, 38]. In normal pregnancies during the third trimester, at least two intraplacental arteries are identified (in most cases 3–5) (Figure 7).

Figure 7 – Color Doppler ultrasound: intraplacental circulation.

In pregnancies complicated by intrauterine growth restriction (IUGR), the intraplacental vascular flow is difficult or impossible to evidence.

It is considered that the insufficient evidencing of intraplacental circulation by color Doppler ultrasound can suggest IUGR and fetal distress.

Three-dimensional ultrasound represents a new group of methods used for the monitoring of pregnancies. Three-dimensional ultrasound examination should be preceded by conventional investigation and can be associated with power Doppler examination. The association of 3D ultrasound with power Doppler provides additional information, by evidencing the vascular pattern of the examined organ [39]. The ultrasound assessment of the placenta is currently considered as important as the morpho-functional study of the fetus [40].

Three-dimensional power Doppler ultrasound should become a routine procedure in the evaluation of the development of placental vascularization during the course of pregnancy. This imaging method should be used at different gestational ages in order to assess the evolution of the placentation process.

The determination of volume and the evidencing of blood vessels by power Doppler represent a first qualitative evaluation stage. Placental vascularization can be subsequently evaluated quantitatively by 3D power Doppler ultrasound, with the determination of three intraplacental vascularization indices [41]. After the estimation of placental volume, the histogram for the determination of vascular indices will be used. These can be calculated using the VOCAL program. There is little information in the literature on the distribution of these placental vascular indices during pregnancy (Figure 8).

Figure 8 – Determination of vascularization indices using the 3D power Doppler histogram.

Over the past years, studies have given an increasing importance to the normal or pathological aspect of the placenta. This is justified by the fact that the placenta, an organ created by pregnancy, ensures fetal-maternal exchange, with direct implications in the development of the product of conception [42].

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