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The Morphology of Villous Capillary Bed in Normal and Diabetic Placenta

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1. Introduction

The functional competence of each organ depends markedly on characteristics of its capillary bed, i.e. volume, structure of the capillary wall, rate of the blood flow, spatial arrangement and relationship to the neighboring structural components of the organ (e.g. epithelium, muscle tissue). The knowledge of the structure, quantity, arrangement and features of microvascular bed of the organ is necessary for the complete understanding of its functions. It is obvious that those characteristics are markedly different among organs (e.g. kidney, liver, endocrine glands, brain, etc.).

In adult organism, the capillary bed of the majority of organs is stable. Active physiological angiogenesis is rare, nevertheless it takes place in some organs of fertile women, and manifests itself either by repeated formation of capillaries in corpus luteum and endometrium or by enlargement of placental capillary bed during pregnancy.

Optimal function of capillaries depends on the appropriate structure of the capillary wall. The microvascular bed, on the other hand, is involved in systemic diseases like hypertension and diabetes mellitus, and its disturbances and damages caused by pathological processes manifest themselves by clinical symptoms.

Maternal diabetes mellitus represents a serious illness threatening both the mother and fetus by serious complications. Metabolic disorders associated with maternal diabetes, however, influence not only the growth and development of fetus, but may have also long-term effects. Its incidence grows with the age of pregnant women. In developed countries, the age of parity of the women shifted to or rather behind their thirtieth year, and therefore the research of maternal diabetes is nowadays particularly topical.

Placenta, which is interposed between mother and fetus, mediates and modifies the influence of maternal diabetes on fetus. It is obvious that placental structure reflects the changed maternal milieu. Placental capillaries play a key role in the transfer of oxygen, nutrients and metabolites between mother and fetus, and any change of their function may have negative effect on fetal well-being. This chapter summarizes the knowledge regarding structural aspects of placental capillary bed in normal human placentas and in placentas from pregnancies complicated by maternal diabetes.

2. Placental capillary bed

Placenta is an organ ensuring and regulating the development of individual *in utero*. Unlike other organs it exists during a short time, holds, either transitorily or continually, the function of developing fetal organs, and is quite unique because of the continual growth and development of its morphology and functional capacity during the whole time of its existence. It fulfils numerous functions, e.g. the bidirectional transport between mother and fetus, secretion of many hormones and other regulating molecules, and so forth. In all those functions its circulatory system, and in particular its capillaries, play very important role.

2.1 Development of the placental vascular bed

In human hemochorial placenta, the fetal blood running through umbilical arteries enters the arteries of the chorionic plate and continues through the vessels of ramified tree-like villi outgrowing from the chorionic plate and (except anchoring villi) floating in maternal blood in the intervillous space. With advanced branching, the villous diameter as well as the diameter of villous vessels gradually decreases, and the thickness and structure of the vascular wall change as well.

Placental villi originate from trophoblast (consisting of external syncytiotrophoblast and internal cytotrophoblast) and extra-embryonic mesenchyme. In connection with the formation of embryonic circulatory system, the vessels start to differentiate within the villous mesenchyma in the 3rd week. Those villi called tertiary or mesenchymal villi repeatedly branch out, and are forerunners of other villous types. From the 6th week to the end of 2nd trimester, a part of mesenchymal villi differentiates into immature intermediate villi. During the first and second trimester, further growth and branching of those villi give rise to the furcated stem villi. Numerous mesenchymal villi appear at the tips of stem villi at the beginning of the third trimester. They are precursor villi of mature intermediate villi, which branch subsequently into terminal villi. At the end of pregnancy, terminal villi represent more than one half (55%) of the total number of villi (Castellucci et al. 1990; Benirschke & Kaufmann, 1995; Kingdom et al., 2000; Challier et al., 2001).

The development of placental villous vessels takes place during the whole pregnancy and comprises two periods, vasculogenesis and angiogenesis. Vasculogenesis takes place in the first and second trimester. During this period, the cords of vascular cells differentiate from mesenchymal cells of the villous core and form vascular lumina by dehiscence. Mesenchymal cells are the source of cells for elongation and widening of vessels and give rise also to perivascular cells - pericytes. In stem villi, the vessels become arteries and veins, and smooth muscle cells, myofibroblasts and fibroblasts of their wall are recruited from the villous stroma as well. Angiogenesis, on the other hand, prevails during the third trimester. In this process, new capillaries form by sprouting of already existing villous vessels, and emerging mature intermediate and terminal villi are vascularized this way (Demir et al., 1989). In the normal term placenta, the estimated total length and surface area of villous capillaries are 550 km and 15 m^2 respectively (Burton & Jauniaux, 1995). They contain approximately 25% of fetoplacental blood volume (Luckhardt et al. 1996).

2.2 Structure of the capillary wall in normal and diabetic placentas

The placenta is interposed between mother and fetus. As described above, both the chorionic plate and chorionic villi are derivatives of embryonic structures, and fetal blood

circulates in their vessels. Therefore the placenta and through it the fetus are in contact with all changes, anomalies and irregularities of maternal organism, and the reaction of the fetus on changed conditions of its environment demonstrates itself in placental structure.

Diabetes mellitus represents a serious complication of pregnancy. Maternal diabetes mellitus threatens the pregnant mothers by development of serious complications based on diabetic microangiopathy, e.g. retinopathy, nephropathy, neuropathy, and enhances the risk of congenital defects, macrosomia and perinatal morbidity and mortality of infants. Various forms of diabetes complicate 3-5% of pregnancies. Type 1 diabetes (pregestational onset, insulin-dependent) represents about 10% of the total, the remainder is in the main gestational diabetes, for other forms, e.g. type 2, are rare (Hájek et al., 2004).

2.2.1 Light microscopy

Maternal diabetes mellitus changes structural features of the placenta. As shown using quantitative method, the consistent organization of villi inside the cotyledon, i.e. occurrence of shorter villi in the centre and longer villi in periphery, is disrupted, and villi (and villous vessels, as deduced by authors) are more branched in diabetic placentas (Bjork & Persson, 1984). The analysis performed by scanning electron microscopy revealed hypo- and hyper-ramified villi in diabetic placentas as compared with normal ones (Honda et al., 1992).

The placental capillary bed is located predominantly in terminal villi, which diameter is 30 – 80 μm in the normal placenta. They are covered by trophoblast consisting of a continual layer of syncytiotrophoblast and sparse cytotrophoblastic cells underneath. Trophoblast is separated by trophoblastic basal lamina from the villous core. It consists of the small amount of loose connective tissue and villous capillaries. Capillaries, lying mostly under trophoblast, display very variable diameter, the majority of them is sinusoidally dilated. Trophoblast covering capillaries is often reduced to a thin nuclei-free cytoplasmic layer of syncytiotrophoblast, which form with the capillary wall a vasculosyncytial membrane. The mean thickness of the barrier between maternal and fetal blood is about 4 μm in normal term placenta, (Mayhew et al, 1984; Burton et al, 1987), nevertheless markedly thinner vasculosyncytial membranes are considered as the sites of preferential transport (fig. 1).

Conventional light microscopic examination does not show striking and typical morphological differences between normal and diabetic placentas, nevertheless certain pathological changes are observable especially in terminal villi. Although a little amount of pathological forms of terminal villi may be found also in placentas from uncomplicated pregnancies, a variable proportion of pathologicaly changed villi appears in each diabetic placenta despite the type of diabetes (Fox & Sebire, 2008). One of structural changes concerns the villous size. It looks more variable at first glance, and as shown by measurement, the mean diameter of villi is greater in diabetic placenta (Emmrich & Müller, 1974). Based on the appearance of villi looking similar to villi from earlier stages of gestation, and on decreased formation of terminal villi, a delayed villous maturation is commonly diagnosed in diabetic placenta. A lot of signs, i.e. more frequent syncytial knots, more prominent cytotrophoblastic cells, more numerous mesenchymal cells in the stroma of some villi, villi displaying stromal oedema or stromal fibrosis, and changed amount, diameter and distribution of villous capillaries may occur and are reported as (of course nonspecific) attributes of placental structure in maternal diabetes (Semmler et al., 1982; Semmler &

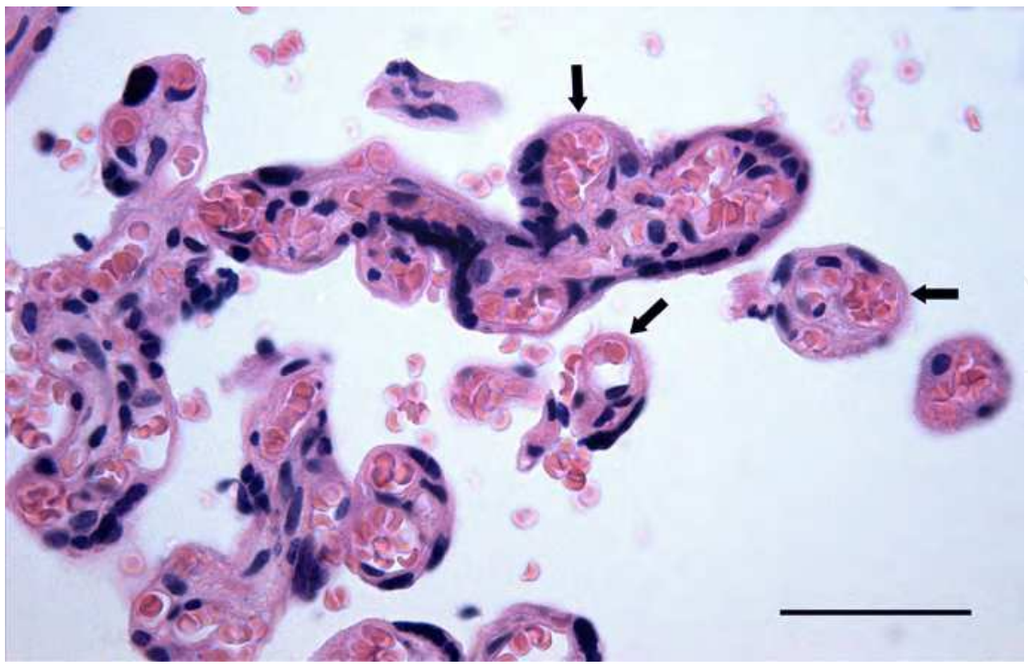

Fig. 1. The picture shows terminal villi of normal human term placenta. Sinusoidally dilated capillaries are in a very tight relationship with trophoblast, arrows indicate vasculosyncytial membranes. Bar = 100 µm.

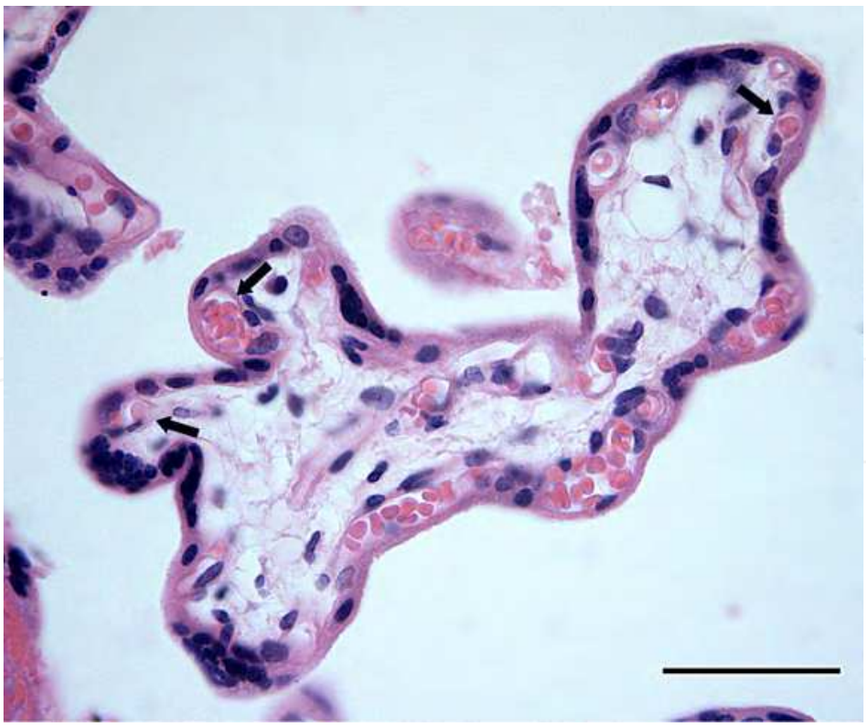

Fig. 2. Hypovascular terminal villi of diabetic term placenta. In the villi of greater diameter and more voluminous stroma (compare with fig. 1), thin capillaries run closely to the trophoblast, in several places as if embedded into it (arrows). Bar = 100 µm.

Emmrich, 1989; Madazli et al., 2008; Higgins et al., 2011). As demonstrated on the production of some placental proteins (e.g. placental alkaline phosphatase, placental lactogen), structural immaturity is associated with concomitant functional immaturity (Greco et al. 1989).

There are two forms of pathological villi differing from normal placental villi in the amount, diameter and distribution of villous capillaries. One form is characterized by sparse capillaries of small diameter located preferentially in a very tight relation to trophoblast, so that large proportion of capillary wall is surrounded by thin nuclei-free layer of syncytiotrophoblast. Voluminous stroma consists of markedly loose meshwork of connective tissue (fig. 2).

In the other type, the capillary profiles are conspicuously numerous, their lumina look often extremely wide, and only small amount of loose stroma is discernible (fig. 3). The thickness of villous trophoblast is markedly reduced, and a thin nuclei-free layer of syncytiotrophoblast covers the majority of capillaries. These hypervascularized villi occur focally in the placenta, and if their frequency meets the Altshuler´s rule (the presence of more than 10 vascular profiles in more than 10 villi in more than 10 areas of 3 non-infarcted placental areas), this finding is called placental chorangiosis. It is associated with increased risk of adverse perinatal outcomes (Altshuler, 1984).

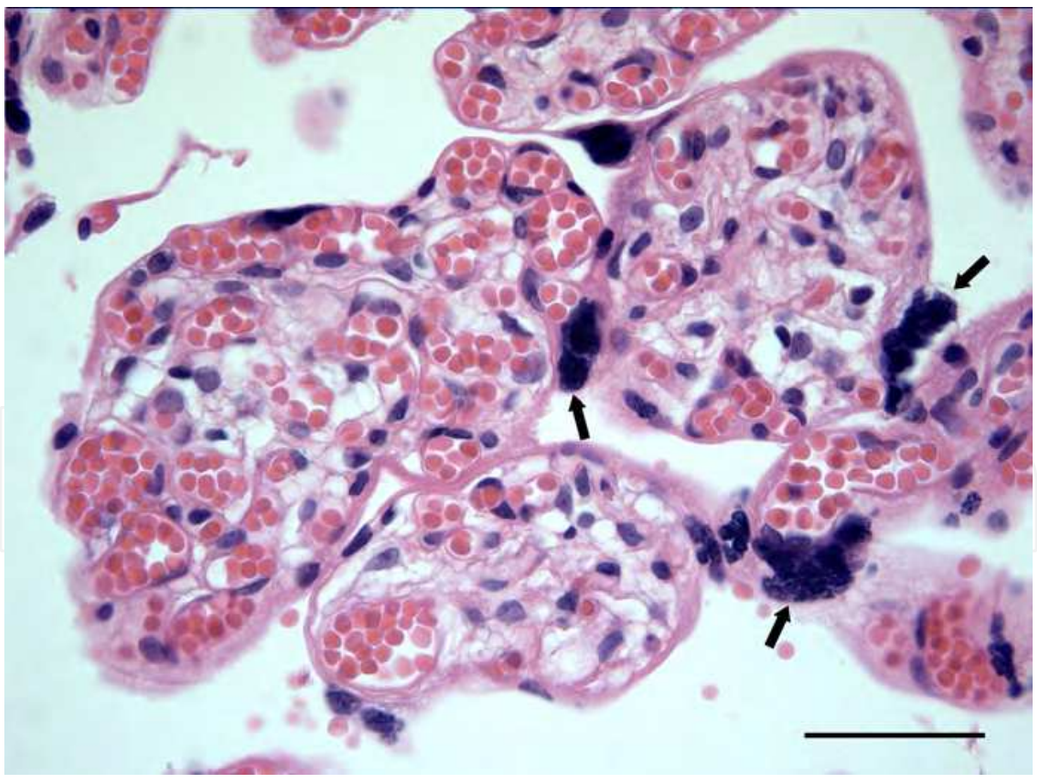

Fig. 3. Hypervascular terminal villi of diabetic term placenta. In the villi of large diameter (compare with fig. 1), very numerous capillary profiles of variable diameter occur in a small amount of stromal connective tissue. Thin trophoblastic layer is nearly completely free of nuclei, which are concentrated in prominent groups (arrows). Bar = 100 μm.

2.2.2 Utrastructure of the placental capillary wall

The structure of the wall of placental capillaries is consistent with its function, i.e. regulator of the bidirectional transport between mother and fetus and component of placental barrier. The capillary wall consists of endothelial cells and pericytes. The endothelium is of the continuous type. Individual endothelial cells are connected each to other with tight and adherent junctions ensuring cell-to-cell adhesion and regulating capillary permeability (Leach & Firth, 1992; Eaton et al., 1993). The abluminal surface is covered by basal lamina, which is divided into two layers where the cell bodies and projections of pericytes are interposed. In that part of capillary wall adjacent to the trophoblast, the pericyte projections are usually missing, and basal laminas of trophoblast and endothelium may fuse. In many instances only thin nuclei-free layer of syncytiotrophoblast covers the capillary, and those segments correspond to vasculosyncytial membranes (fig. 4).

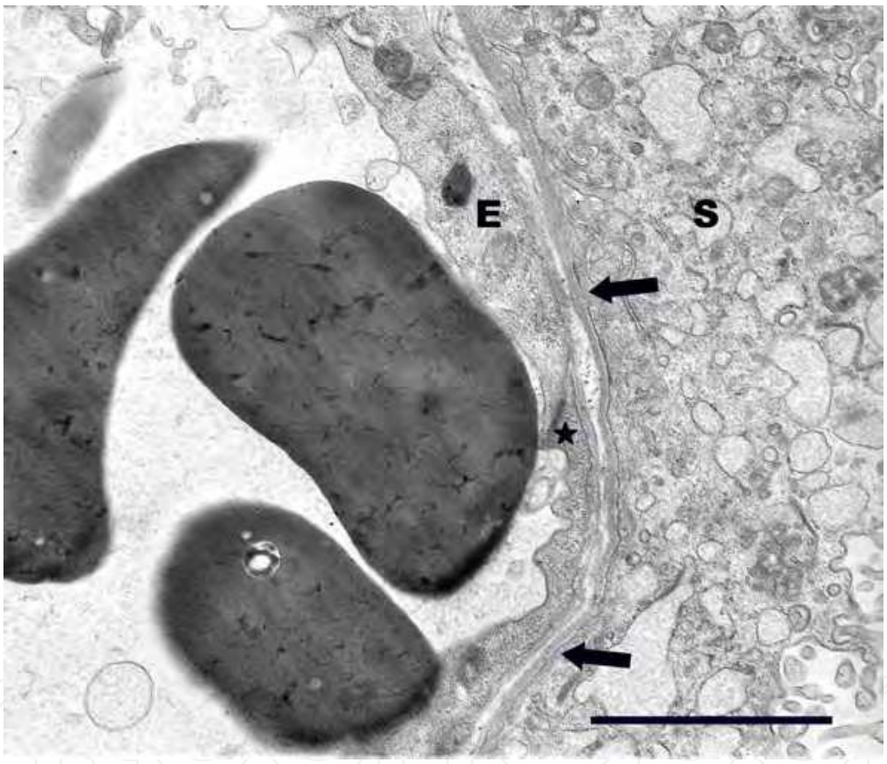

Fig. 4. A part of the capillary wall lying in a tight relationship to the syncytiotrophoblast at the site of vasculosyncytial membrane. No projections of pericytes are interposed between endothelium (E) and syncytiotrophoblast (S), which basal laminas tend here and there to fuse (arrows). Asterisk = adherent junction between endothelial cells. Bar = 2 μm.

Pinocytotic and other vesicles and large amount of fine filaments dominate the submicroscopic picture of typical thin endothelium. In some instances, the endothelial cells are prominent or bulging into the lumen, so that some capillaries may have a slit-like lumen only. The peripherally arranged heterochromatin and nucleoli in nuclei together with organelles (granular endoplasmic reticulum, Golgi aparatus) occurring in cytoplasma indicate an active cellular stage probably associated with current angiogenesis (fig. 5).

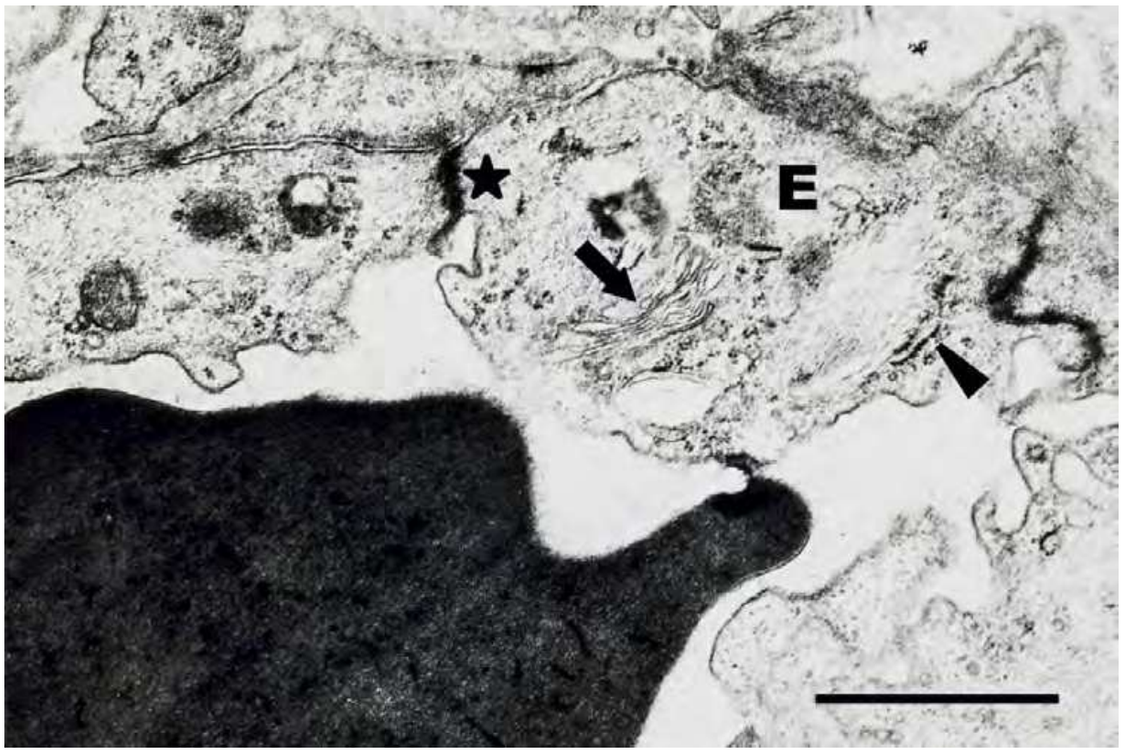

Fig. 5. Golgi apparatus (arrow) and granular endoplasmic reticulum (arrowhead) appearing in capillary endothelium (E) of term placenta. Asterisk = adherent junction between endothelial cells. Bar = 1 μm.

The phenotype of placental microvascular endothelium is characterized by expression of numerous molecules, e.g. von Willebrand factor, endothelial and inducible nitric oxide synthases, caveolin 1, CD 31, CD 34, ICAM 1, PECAM 1 (Dye et al., 2001), and differs from the endothelium of placental macrovessels (Lang et al., 2003). As reported in a current paper, the expression of some of them, in particular the nitric oxide synthase, is modified by maternal diabetes (Sobrevia et al., 2011).

Only little attention was paid to placental capillary pericytes up to the present, even in otherwise exhaustive papers dealing with the villous ultrastructure (e.g. Haust, 1981). According to some authors, pericytes do not display different structure in normal and diabetic placentas (Kacemi et al., 1999), although certain differences of the shape of their cytoplasmic projections were described in pathological placentas including those from pregnancies complicated by maternal diabetes (Jones & Desoye, 2010). Vimentin and smooth muscle actin, but no desmin were demonstrated in the cytoplasm of pericytes in normal as well as diabetic placentas (Kučera et al., 2010).

Being a component of placental capillaries, pericytes have a potential to react on changes of placental environment in maternal organism, e.g. hypoxia. To date, this topic was studied in two papers comparing the pericyte coverage between placentas from lowland and high altitudes, and between normal and diabetic placentas. Placental capillaries from high altitudes were found less covered by pericytes than those from lowland (Zhang et al. 2002). It is evident, that such decrease of thickness of the barrier separating maternal and fetal blood is an appropriate adaptation on low oxygen pressure. On the other hand, no

difference was found in perivascular cell coverage between normal placentas and placentas in type 1 diabetes as well as between placentas of diabetic mother with normal and pathological levels of glycated hemoglobin (Kučera et al., 2010).

Although the basic structure of villous capillaries is similar, the comparison of capillaries of normal and diabetic placentas has shown further certain differences. For instance, glycogen granules are commonly found in capillary endothelium of normal placentas. In the villi of diabetic placentas, a higher content of glycogen deposits was described in endothelial cells and pericytes (and also stromal cells) of diabetic villi (Haust, 1981; Asmussen, 1982; Jones & Desoye, 1993).

A more frequent incidence of extravascular red blood cells in terminal villi of diabetic placentas was documented by electron microscopy (Okudaira et al., 1966; see also fig. 6). It may be a consequence of perturbations of molecules forming adherent junctions at the contact of endothelial cells. Those junctions were found less stable in placentas from pregnancies complicated by both gestational and type 1 diabetes mellitus (Babawale et al. 2000; Leach et al., 2004).

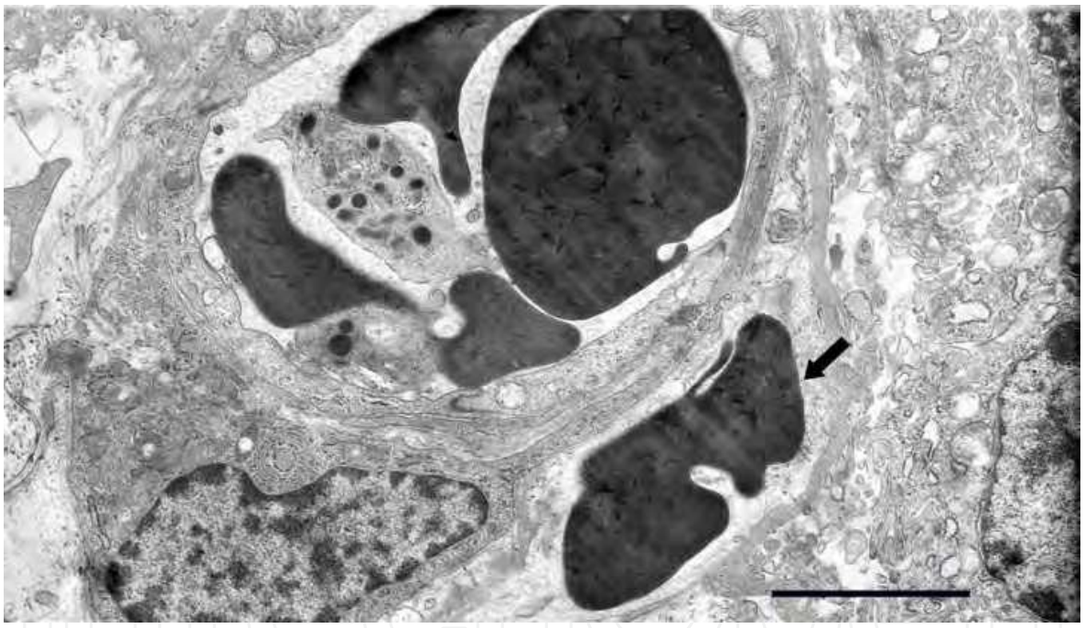

Fig. 6. Extravascular erythrocytes (arrow) are regularly found in diabetic term placenta. Bar = 2 μm.

2.2.3 Capillary basal lamina

The capillary basal lamina may be a compact layer surrounding the capillary (fig. 4), or appears in several loosely arranged stripes of basal lamina material in the neighborhood of capillaries. The latter may be found in normal placentas too, but is described as more frequent in diabetic villi (Okudaira et al., 1966; Jones & Fox, 1976; Asmussen, 1982; see also fig. 7). It is not quite easy to explain the origin of such arrangement, but taking into account that placental capillaries are dynamic structures, we assume that angiogenesis and apoptosis regulate their amount and volume.

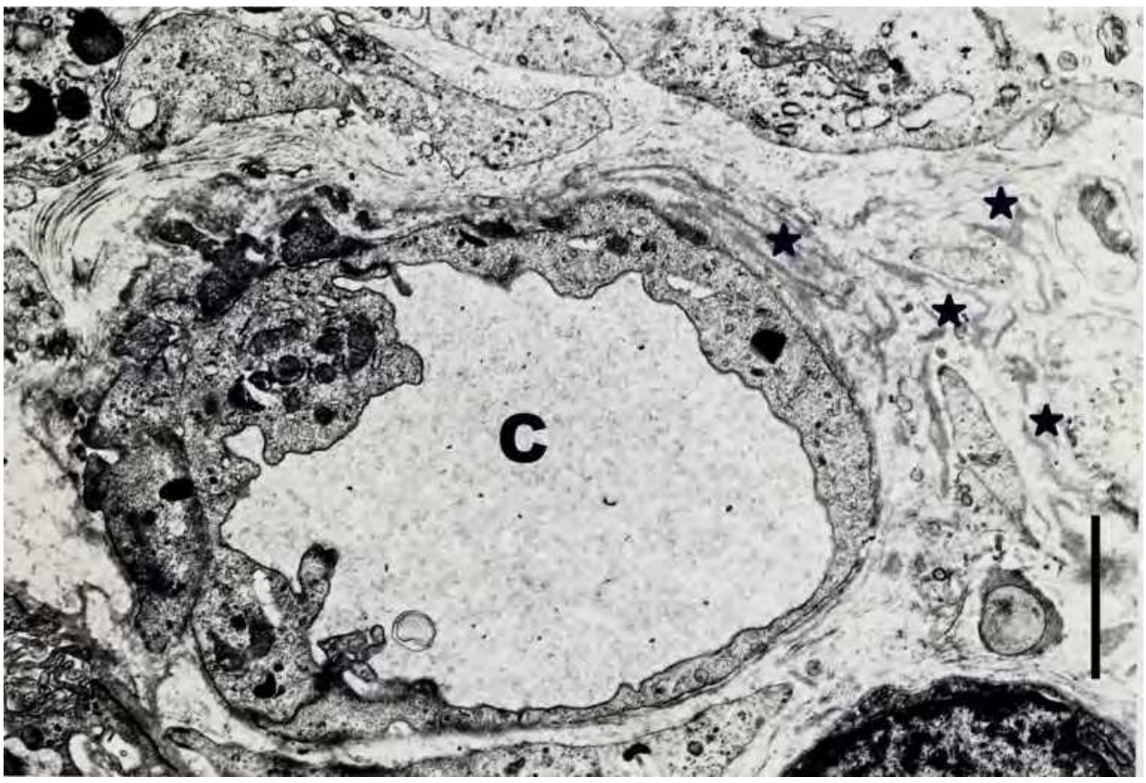

Fig. 7. Loosely arranged strips of the material of basal lamina (asterisks) occur in the neighborhood of diabetic placental capillary (C). Bar = 2 μm.

As documents the occurrence of apoptotic marker caspase 3, apoptosis takes place in placental capillary bed and manifests itself either in individual endothelial cells and pericytes or in larger patches of capillary wall (fig. 8). Stripes of basal lamina material may be probably the only residuals of previous segments of capillary wall. The only quantitative study comparing apoptosis in villous capillaries has shown that the apoptotic activity in the capillary bed of diabetic placentas seems to be higher, but the difference between normal and diabetic placentas as well as between placentas of diabetic mothers with normal and increased levels of glycated hemoglobin was not found statistically significant (Kučera et al., 2011).

Diabetes mellitus has been linked to accelerated microangiopathy, and thickenning of the capillary basal lamina has been considered as its manifestation. In descriptive studies based on qualitative electron microscopic analysis, discrepant opinions were reported regarding the thickness of the capillary basal lamina in diabetic placenta. However, only the measurements have shown that the mean thickness of capillary basal lamina is significantly lower in placentas of mothers suffering from type 1 diabetes mellitus (Emmrich et al., 1976; Jirkovská, 1991). In order to explain this phenomenon we have to take into account that placental capillaries belong to the fetoplacental circulation. Fetal pancreas produces sufficient amount of insulin, and thus fetus is not a diabetic. Therefore, no reason exists for development of diabetic microangiopathy in fetoplacental microvessels. The lower mean thickness of capillary basal lamina, on the other hand, may be a consequence of higher proportion of newly formed capillaries. Enhanced angiogenesis has been repeatedly documented in the villi of diabetic placentas in studies applying quantitative morphological methods (see further).

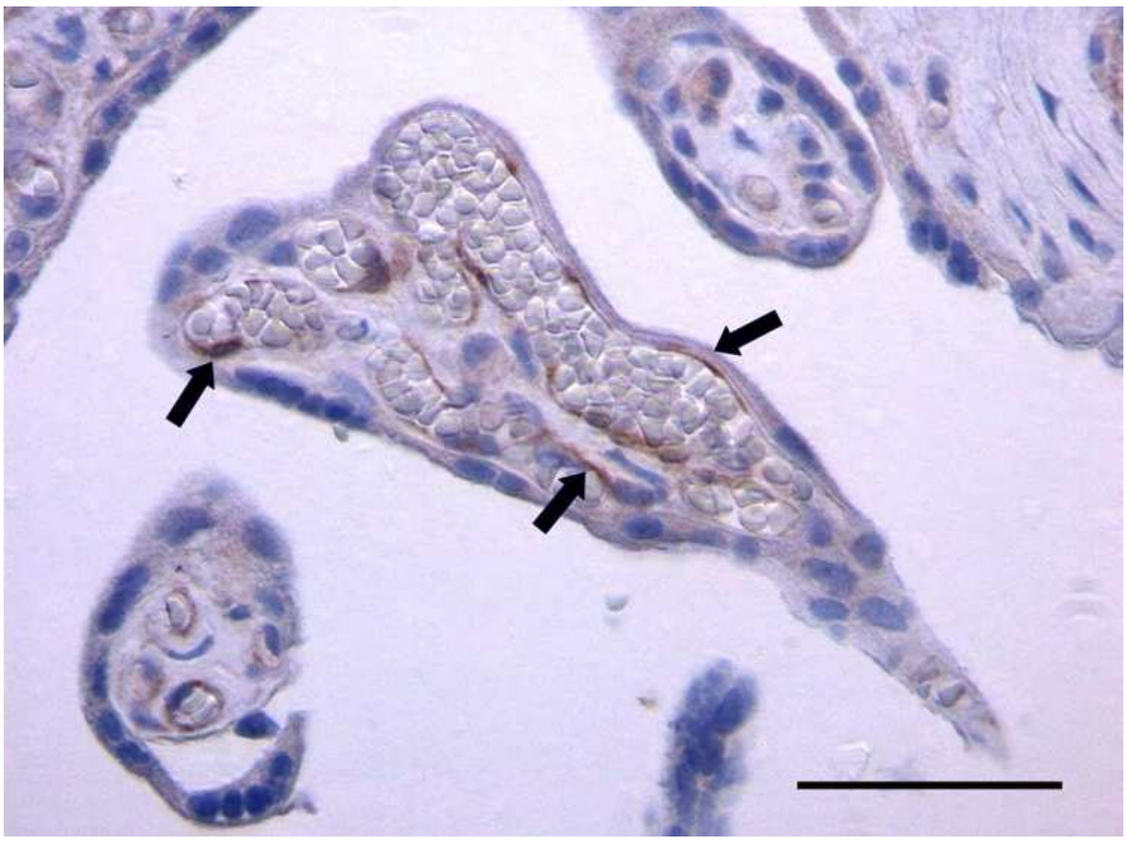

Fig. 8. Apoptosis in the villous capillary wall in diabetic placenta demonstrated by the occurrence of caspase 3 (arrows indicate brown reaction product). Bar = 100 μm.

2.3 Quantitative comparison of structural differences between normal and diabetic placentas

The quantitative approach to the explanation of the connections of placental morphology and function surely deserves our attention too. The effort to quantify histological structure of placenta and to compare normal organs and organs associated with pathologies of pregnancy brought a lot of useful information and enhanced our understanding of placental function. On the other hand, due to the progress in the treatment of maternal diabetes and the evolution of methodology used for such studies in the past four decades, results of those studies are often hardly comparable because of heterogeneous severity of diabetes, different standards of treatment of pregnant diabetic women, metabolic control achieved during pregnancy in examined diabetic mothers, different strategies of tissue sampling and processing, and different designs and methods of evaluation.

A simple microscopic evaluation performed mostly by a pathologist blinded to clinical data belongs to the traditional approaches. Two studies applying this method considered the decreased proportion of the vascular component in diabetic placental villi as indicative for more severe placental maturation disorders, and the occurrence of signs of placental maturation disorders as dependent on the quality of metabolic control (Semmler et al., 1982; Semmler & Emmrich, 1989). Results of the study, published in a more recent paper, were

obtained using similar method. The authors concluded that villous immaturity and chorangiosis are increased in placentas in type 1 diabetes associated with both the large-for-gestational- age and appropriate-for-gestational-age infants (Evers et al. 2003).

Another approach, how to quantify the structure, is morphometry and stereology. Here are applied objective methods of measurement in order to either assess different parameters, e.g. villous calibre, trophoblast thickness, number and size of fetal vessels, or to estimate total numbers, volumes, surface areas, etc. A lot of articles dealing with quantification of placental structure are available in the literature, and many of them pay the attention to the comparison of parameters between normal and various types of diabetic placenta.

In addition to the already mentioned papers, further results of quantitative studies of diabetic placenta are presented as follows.

The total placental surface area, a key parameter of placental transport capacity, was estimated as greater in diabetic placentas (17.3 m^2) then in controls (11.4 m^2) as well as the proportion of parenchymal components (including capillaries) was found higher in diabetic placentas (Boyd et al. 1986).

In their studies, Geppert et al. (1982) and Jirkovská et al. (1994) have found significantly lower vascularization of the placental villi (defined as the area of capillary cross-sections within the villus divided by the area of the villous cross-section) in examined diabetic placentas. On the contrary, Teasdale found greater total capillary surface areas and more numerous capillary profiles per unit area in placentas of pregnant mothers suffering from both the gestational and type 1 diabetes (Teasdale, 1981; Teasdale, 1983; Teasdale, 1985).

Various placental parameters were compared, and quantitative structural changes of diabetic placentas were reported in other studies. The attention was paid of course to placental vascular bed, especially to villous capillaries. The greater total volume, length, surface area and mean diameter of capillaries have been reported in placentas in type 1 diabetes as well as in gestational diabetes, and those parameters were found also dependent on the sex of newborn, i.e. greater in placentas of male fetuses (Mayhew et al., 1993; Mayhew et al., 1994). Those findings were corroborated in later study (Mayhew, 2002). On the contrary, some authors (Jauniaux & Burton, 2006; Nelson et al., 2009) have found no differences of total capillary volumes and capillary surface areas between control and diabetic placentas. To date newest article reports greater placental capillary volumes, lengths and surface areas in type 1 and type 2 of maternal diabetes (Higgins et al. 2011).

Based on these, although rather ambiguous data, we may conclude after all that the angiogenesis is more active in diabetic placenta.

2.4 The spatial organization of villous capilary bed

2.4.1 The three-dimensional arrangement

In the placenta, the capillary bed play a key role in maternofetal transport, and thus acts as a decisive factor in the appropriate intrauterine development of fetus. Fetal blood runs in fetoplacental capillaries, but unlike other organs, the oxygen is not extracted there from erythrocytes. To the contrary, it diffuses through trophoblast and capillary wall, and binds fetal hemoglobin. It is obvious that the amount of oxygen available for oxygenation of fetal

hemoglobin depends on many factors, the oxygen concentration in maternal blood, the total surface areas of trophoblast and capillary wall, and the thickness of placental barrier being the main. The proper blood flow in placental microvessels and macrovessels then ensures that the fetus obtains adequate amount of oxygen and nutrients. As the blood flow follows other physical principles in macrovessels than in microvessels, the correct understanding of features and function of placental microvascular bed, in particular capillaries, requires knowledge on its dimensions and spatial arrangement.

Some papers dealing with spatial organization of placental villous microvessels have been published in last five decades, but their paucity gives evidence that such study is quite a task. Moreover, their results are hardly comparable because of placental material of different stages of gravidity taken into study and various technical tools used.

Two of authors dealing with this subject applied injections of dye solutions into placental vessels and documented their distribution by photomicrographs (Crawford, 1956; Boe, 1969). Based on their findings, they created quite different schemes of villous capillary bed. According to Crawford´s conclusion, the long non-branched capillary runs garland-like through series of terminal villi and forms hairpin-like loops inside them (fig.9). The author does not describe sinusoidal dilations of capillaries.

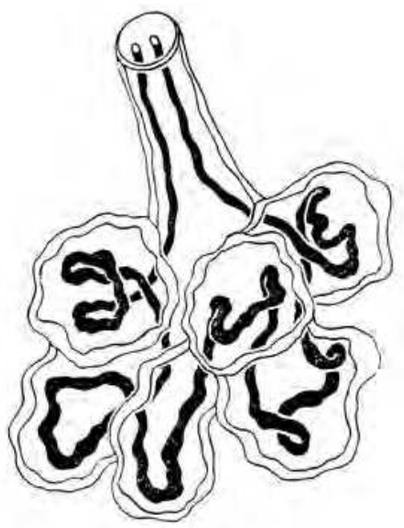

Fig. 9. The arrangement of villous capillaries according to Crawford (from Crawford, J.M. (1956). The foetal placental circulation. IV. The anatomy of the villus and its capillary structure. *J Obstet Gynaecol Br Emp, Vol.* 63, No. 4, pp. 548-552, John Wiley and Sons Ltd., with permission).

To the contrary, Boe demonstrated capillaries in densely arranged terminal branches of chorionic villi in the placenta at the end of first trimester. Their dense webby villous capillary networks connect dense, richly branched paravascular capillaries of so called immature intermediate villus. Segments of paravascular capillaries running at the base of terminal branches act as arterial-venous shunts. In accordance with other authors (Crawford, 1956; Arts, 1961), Boe considered the terminal villus as independent circulatory unit (fig. 10).

Unlike Boe´s scheme, the Arts´s (Arts, 1961) model of vessels in mature intermediate and terminal villi, based on the analysis of corrosive casts, is poor in paravascular capillary

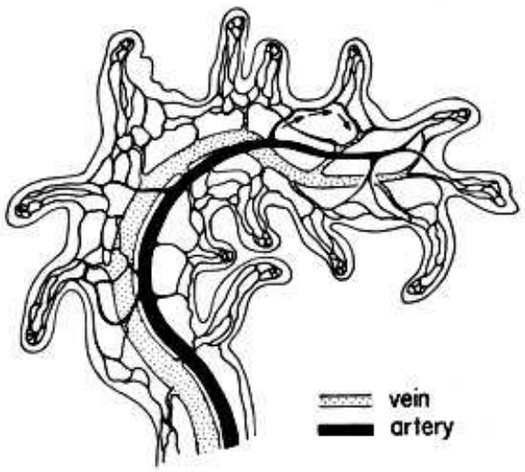

Fig. 10. The Boe´s model of the arrangement of placental microvascular bed (from Boe, F. (1969) Studies on the human placenta. III. Vascularization of the young foetal placenta. A. Vascularization of the chorionic villus. *Acta Obstet Gynecol Scand,* Vol. 48, No. 2, pp. 159-166, John Wiley and Sons Ltd., with permission).

network. Capillaries of terminal villi arise directly from arteries. Their segments are arranged parallel to the axis of villus and interconnected with short connections. The blood leaving terminal villi runs directly into veins. The sinusoidally dilated capillary segments are interpreted as sections of lower blood pressure and slow blood flow, which are favourable for materno-fetal transport (fig. 11).

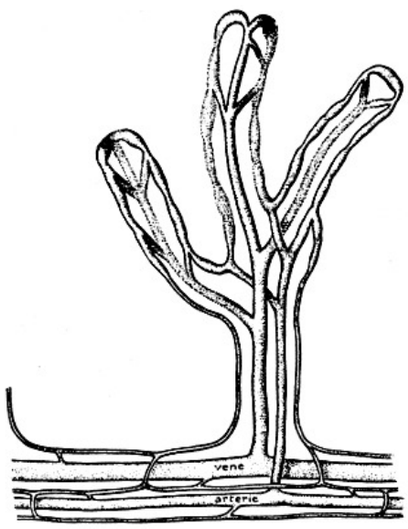

Fig. 11. A schematic representation of the vascular bed of mature intermediate and terminal villi according to Arts (from Arts, N.F.T. (1961) Investigations on the vascular system of the placenta. I. General introduction and the fetal vascular system. *Am J Obst Gynec*, Vol. 82, No. 1, pp. 147-158, Elsevier, with permission).

The analysis of corrosive preparations by scanning electron microscope showed the arrangement of villous capillaries more precisely, however due to the method, the relationships of capillaries and other tissues forming the villus were not preserved (Leiser et al., 1985; Kaufmann et al., 1985; Akiba et al., 1987; Burton, 1987).

Another model of placental microvascular bed was based on scanning electron microscopy of corrosive casts combined with physical 3D reconstruction from photomicrographs of serially cut histological sections of placental villi (Leiser et al., 1985; Kaufmann et al., 1985). This model represents a mature intermediate villus and its branches - terminal villi, and their vessels. The capillaries of terminal villi are predominantly represented by sinusoidally dilated U-like capillary loops, which branches are only seldom interconnected with a short capillary segment. No arterial-venous shunts were shown, but signs of current angiogenesis in human term placenta, i.e. blind capillary sprouts, were described in this study for the first time. The wavy course of long and rarely branched capillaries running through serially arranged terminal villi suggests to a certain degree the Crawford´s scheme.

As documented above, the successful representation of three-dimensional structure depends on the methods available. Nevertheless, regardless the technical progress, the making of 3D reconstruction of any biological object is very laborious and time consuming in any case. Usually it consists of serial sectioning of the object, appropriate staining of sections, acquisition of images by a microscope, alignment of images, generation and conversions of initial data, and application of relevant 3D rendering software. Many of those steps may create artifacts. The application of confocal microscopy eliminates problems with the alignment of serial physical sections, as it enables to acquire series of perfectly aligned optical sections inside thick physical section (fig. 12). Due to its advantages, the confocal laser scanning microscope has been used repeatedly for acquisition of initial data for 3D reconstruction of organ microvessels, e.g. for analysis of microvascular bed of human liver (Oikawa et al., 1999), for developmental study of vascular bed during the morphogenesis of intestinal villi (Hashimoto et al. 1999) or for studies on spatial organization of chick mesonephros (Jirkovská et al., 2001; Jirkovská et al., 2005).

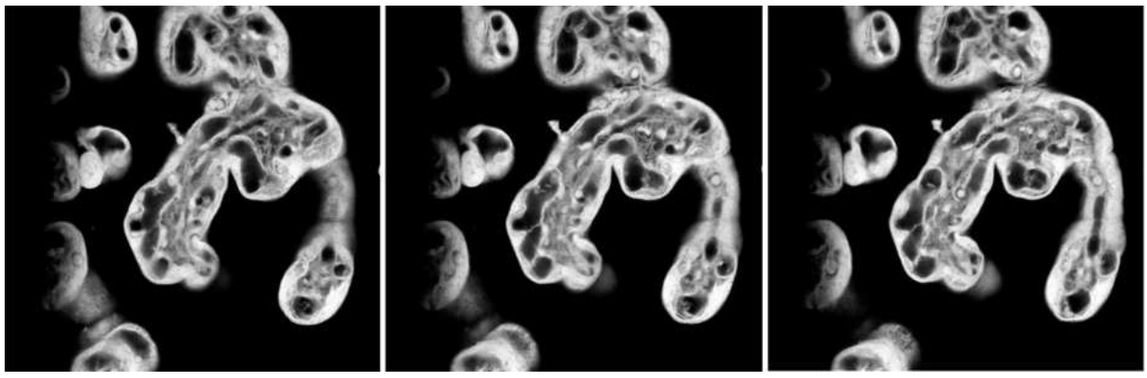

Fig. 12. Three perfectly aligned serial confocal optical sections of placental villi were taken 2 μm apart. Note very well discernible villous structure after fixation in a fixative with added eosin.

Confocal microscopy was also a key method used in our studies of villous capillary bed in normal and diabetic placenta. Its application together with the appropriate software enabled to create 3D reconstructions of sufficient amount of villi, and thus to visualize various arrangements of villous capillaries.

As shown in pictures of three-dimensionally reconstructed villous capillaries, their size, shape and arrangement displays great variability. Two simplest types represent a U-like loop and a Y-like bifurcation. Capillary segments of those beds are usually slightly wavy, and their course is more or less parallel with the axis of villus. In more complicated beds, the longitudinally oriented segments are interconnected with short connections. For the purpose of topological description, they are called "redundant", as they can be removed without disconnecting the villous capillary bed. It is evident that they are by no means redundant from the functional point of view (fig. 13).

Individual terminal villi, arising from the mature intermediate villi, are usually of cylindrical shape, and their capillaries arise from the vascular bed of mature intermediate villi. Terminal villi may also form cluster-like structures, and their capillaries are interconnected so that they form complicated capillary networks (fig. 14).

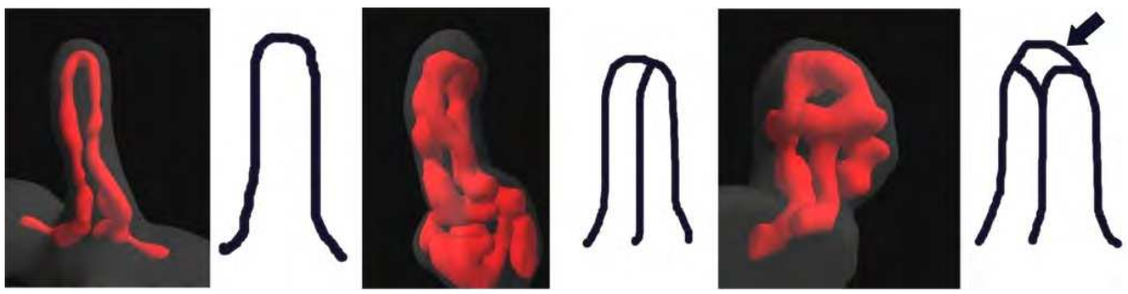

Fig. 13. Three-dimensional reconstructions and topological schemes of the U-like and Y-like villous capillaries, and of a capillary bed containing one redundant connection (arrow).

Terminal villi of more complicated shape originate from the pre-existing villus by a trophoblast protrusion driven by angiogenesis Their capillary bed originates from the capillary bed of pre-existing villus and is complex (fig. 15).

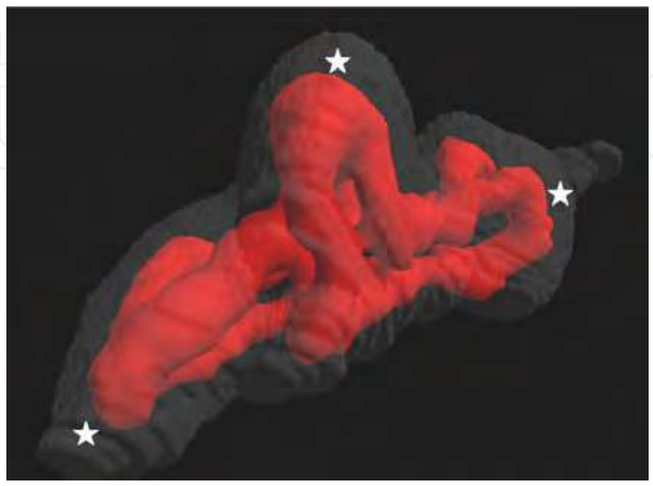

Fig. 14. An example of three villi (asterisks) in a cluster, and their interconnected capillaries.

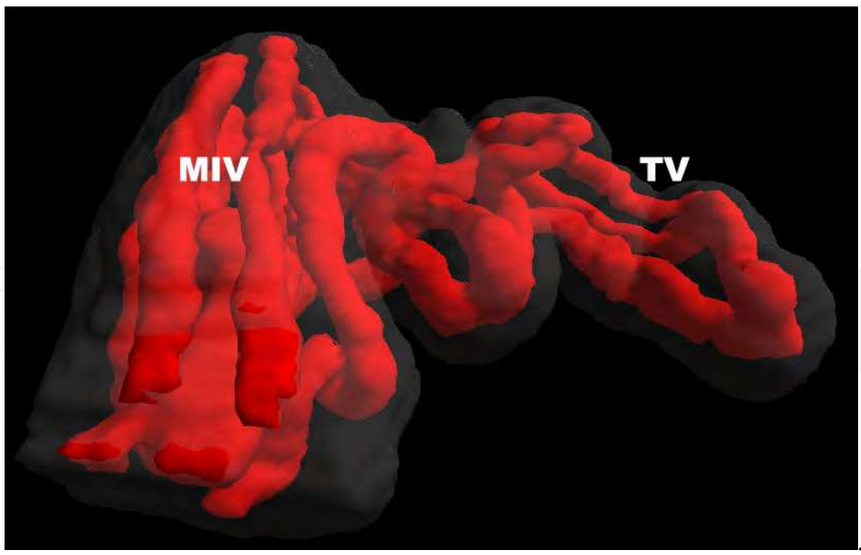

Fig. 15. A branched terminal villus (TV), which complex capillary bed is supplied from vessels of the mature intermediate villus (MIV).

The used methods of confocal microscopy and 3D reconstruction enabled us also to demonstrate that placental villous capillaries grow by elongation as well as by sprouting of pre-existing capillaries until term (Jirkovská et al, 1998; Jirkovská et al., 2002, Karen et al, 2003; Jirkovská et al., 2008). This finding challenged the hypothesis, expressed by some authors, that placental angiogenesis shifts from the sprouting to the elongating angiogenesis after the 25th week of gestation (Kaufmann et al., 1985; Mayhew, 2002 a; Mayhew, 2002 b).

In diabetic placentas, the spatial organization of villous capillaries was found mostly similar to the normal placenta, but there were some differences concerning shapes of villi. As shows the example in fig. 16, the mature terminal villi of normal placentas are long and slender. Their capillaries have straight or slightly waved course and are usually branched. They are arranged tightly and parallel to the villous axis.

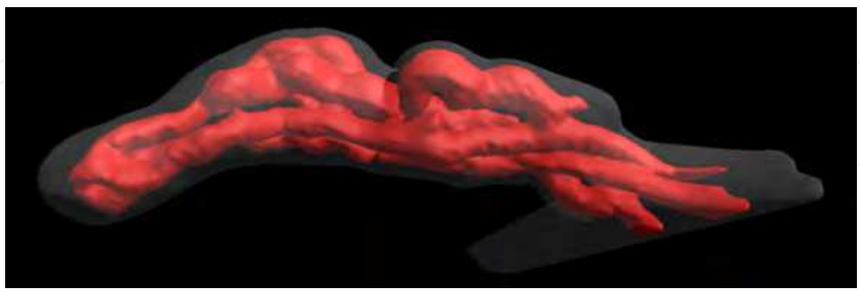

Fig. 16. Three-dimensional reconstruction of a normal placental terminal villus shows tightly arranged parallelly oriented villous capillaries.

Pathological forms of villi in diabetic placenta are rather of round shape. In hypovascularized villi, the 3D reconstruction revealed a conspicuously wavy course of thin capillaries (fig. 17), whereas hypervascularized villi displayed markedly wavy course of extremely distended capillary segments (fig. 18).

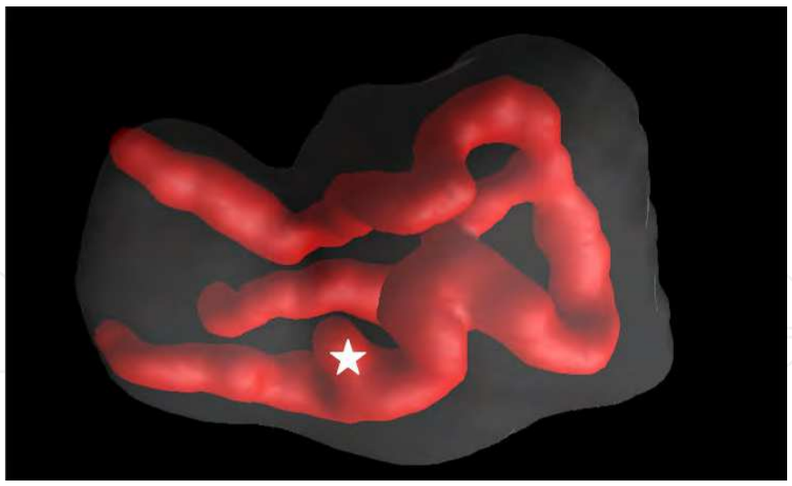

Fig. 17. Three-dimensional reconstruction of a hypovascularized villus of diabetic placenta. The capillaries are conspicuously wavy, asterisk indicates a capillary sprout.

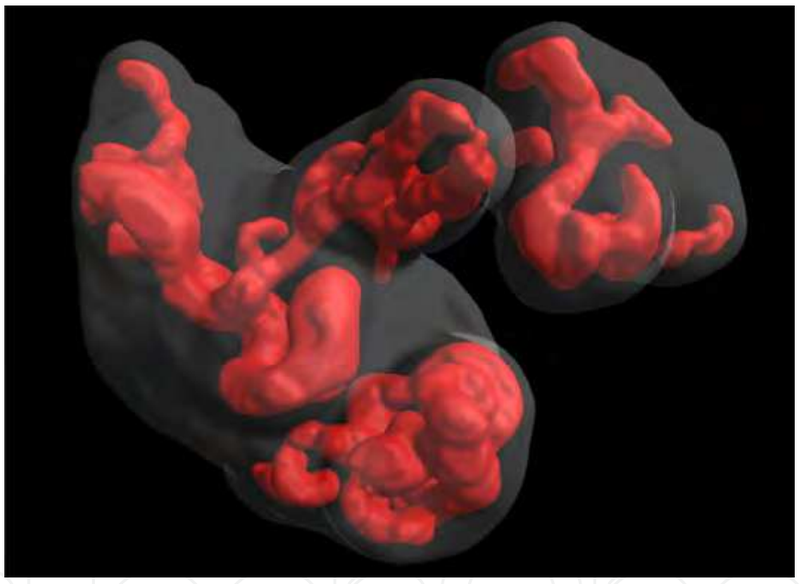

Fig. 18. Three-dimensional reconstruction of a hypervascularized villus of diabetic placenta shows capillaries of wavy course and often very large diameter.

2.4.2 The branching of villous capillaries in normal and diabetic placentas

As mentioned above, the majority of papers regarding quantitative comparison of capillary bed in normal and diabetic term placenta documented that maternal diabetes enhances placental angiogenesis. However, they gave no information on its consequences for spatial arrangement of capillaries.

The use of confocal microscope made possible not only to demonstrate spatial arrangement of villous capillaries, but also to perform quantitative analysis of the capillary branching in ample numbers of villi from normal and diabetic placentas using methods of topological schemes (fig. 13). These schemes of various forms of villous capillary beds were statistically

analyzed, and mean numbers of redundant connections per villus and ratios of villous capillary beds without and with redundant connections were finally summarized in table 1. The results achieved in control placentas were significantly different from results achieved in placentas from pregnancies complicated by both gestational diabetes (Jirkovská et al., 2002) or type 1 diabetes (unpublished data). On the other hand, the results obtained in diabetic groups showed no significant differences.

These data indicate that enhanced capillary branching is a common manifestation of maternal diabetes in placental structure. This way, by means of placenta, the fetus probably reacts on adverse intrauterine environment caused by maternal metabolic disorder. It threatens the fetus above all by hypoxia (Mayhew et al., 2004), and the formation of new capillary segments represents undoubtedly a compensatory mechanism. Those new segments not only enlarge the capillary surface area, but their growth is also a driving force of the formation of new villi**,** and thus enlargement of the area of syncytiotrophoblast. The fact that the quantitative data concerning capillary branching are similar in both diabetic groups suggests that both types of maternal diabetes are equally serious from the fetal point of view, although the gestational diabetes represents only a transitory metabolic disorder for the mother.

Group (number of placentas)	**Control (9)**	**GDM (11)**	**DM 1 (7)**
Mean number of connections per villus	0,229 ± 0,092	0,449 ± 0,114 *	0,505 ± 0,278 *
Ratio of villi without connections	0,817 ± 0,087	0,632 ± 0,044*	0,596 ± 0,167 *
Ratio of villi with one connection	0,184 ± 0,083	0,308 ± 0,074	0,284 ± 0,144
Ratio of villi with two connections	0,002 ± 0,004	0,062 ± 0,043*	0,063 ± 0,058 *
Ratio of villi with three or more connections	0,00	0,017 ± 0,023	0,021 ± 0,044

Table 1. Summarized results of the analysis of villous capillary branching in control placentas and placentas from pregnancies complicated by gestational (GDM) or type 1 diabetes mellitus (DM 1). * = the value is significantly different from the control group.

3. Conclusion

The aim of this chapter was to summarize the knowledge regarding structural differences of the capillary bed of normal and diabetic term placenta. This overview comprises data obtained by conventional light microscopy and electron microscopy, by methods of quantitative morphology with emphasis on morphometry and stereology, and by methods based on confocal microscopy. It has been shown that structural differences between normal and diabetic placenta demonstrate themselves in higher degree of immaturity of diabetic villi, in different degree of villous capillarization, in different diameter of capillaries, and in the occurrence of basal lamina material and extravascular erythrocytes in the villous stroma. Three-dimensional reconstruction of villous capillaries revealed markedly waved thin capillaries in hypovascularized diabetic villi and markedly waved capillaries with conspicuously dilated segments in hypervascularized diabetic villi, as compared with villous capillaries of normal placenta. The majority of structural differences are of quantitative nature. It demonstrates itself in larger diameter of villi, in thinner capillary basal lamina, and in more branched capillaries of terminal villi. All this knowledge might

and should be a challenge for further research, e.g. of functional consequences and molecular mechanisms leading to those structural changes.

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Recent Advances in Research on the Human Placenta

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