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The structural heterogeneity of chorial villi phenotype determined by angiogenesis. Implications in legal pathology

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Abstract: Micro anatomic phenotype of chorial villi can be achieved only by means of a rigurous evaluation of its structural elements: trophoblast, vascular and mesenchyme. The authors proposed themselves to study the reciprocal relations between syncytiotrophoblast, fetal sinusoid capillaries and argentic collagen fiber fascicles inside chorial villi depending on angionesis process. The research was carried out on human biologic material using placenta fragments during 28-37 weeks of gestation. The authors consider that the collagen IV stereo distribution inside the vascular pedicle of the terminal villi, contributes to the stability, biodynamic and biokinematics of villi phenotype that is determined by branching or non branching angiogenesis.

The personal results have a great value for stating the variability limits of terminal villi phenotype in ortology as well as in general or forensic pathology.

Key Words: terminal villi, angiogenesis, collagen IV, villi phenotype

The chorial villi phenotype is determined either by vasculogenesis either by angiogenesis. It is considered that until the end of gestation, the blood capillaries network reaches 550 km in length and 15 m2 in surface (Burton and Jauniaux, 1995) [7]. Angiogenesis plays an important role in formation and remodeling of blood vessels inside human placenta terminal villi.

In the second half of gestation there is a growth acceleration and an increase in number for mature intermediate and terminal villi and for sinusoid blood capillaries (Mayhew, 2002) [22].

Space architecture and micro vascular networks evaluation present a special interest for general development anatomy. For human placenta, capillaries stereo distribution and their implementation inside the chorial villi structures in the last trimester of gestation, still needs further explanations and incites to many questions of functional anatomy:

1. What are the determinant factors for the variability of placenta villi phenotype ?
2. What ensures the perenity of placenta villous structures during gestation ?
3. Are there dynamic structures that can control the blood flow inside villous capillary network ?
4. How is the villous phenotype influenced by time and space genesis, regenesis and remodeling of the villous structures: mesenchyme, trophoblast, blood capillaries and collagen IV ?
5. Where is the location for placenta barrier and how is it structured during gestation dynamics ?
6. Can we individualize and differentiate on the micro anatomic routine sections, the arterial advehent capillaries from the venous revehent ones that belong to the fetus placenta blood system ?

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7. How do interfere the processes of vasculogenesis and angiogenesis during the morphologic and functional intervals of gestation ?
8. Why is it necessary the knowledge of the blood vessels stereo distribution in the anatomic and functional evaluation of human placenta, in ortology and pathology?
9. How are achieved the multiplication and structuring of terminal villi during the third trimester of gestation ?
10. What is the information value of collagen IV distribution inside terminal villi?
11. What is the signification of placenta sinusoid capillaries relations to the following structures: "real sprouting", "syncytial knots" and "syncitial bridge" with normal syncytial nuclei of trophoblast ?

We proposed to achieve the following objectives:

1. The space evaluation of sinusoid blood capillaries inside chorial villi during the third trimester of gestation;
2. The understanding of the reciprocal relations between placenta mesenchyme, sinusoid blood capillaries and villous trophoblast;
3. Collagen IV stereo distribution inside chorial villi;
4. The analysis of ischemia effects on chorial villi;
5. The analysis of spiral distribution of collagen fiber fascicles around pre capillary alanto umbilical blood vessels.

Materials and methods

Our study was performed on tissue fragments harvested from placentas after gestation with variable duration: 28 weeks (6 cases); 32 weeks (8 cases); 36 weeks (7 cases); 37 weeks (5 cases) and 38 weeks (10 cases). Two women presented diabetes. The tissue fragments were processed by micro anatomic techniques of paraffin embedding. The serried sections were stained with Hematoxiline Eosine or processed after Gomori method for collagen fibers argentic impregnation. The iconography was digitally captured.

Results

The structural heterogeneity of chorial villi phenotype determined by angiogenesis during the third trimester of gestation was evaluated by classic micro anatomic methods used in any pathology lab. We grouped our personal result into two chapters: A. Microanatomic analysis of the locations and the relations of sinusoid blood capillaries inside placenta villi; B. Micro anatomic analysis of collagen IV stereo topographic organization for the acknowledgement of its implementation in placenta villi genesis, regenesis and remodeling.

A. The location and the relations of sinusoid blood capillaries inside placenta villi.

The micro anatomic analysis of the locations and the relations of sinusoid blood capillaries was achieved on fragments harvested from placentas with 28 (Figure 1), 30 (Figure 2), 32, 36 (Figure 3) and 37 (Figure 5) weeks of gestation.

On the serried sections through placentas with 28 weeks of gestation we noticed mature intermediate and terminal villi sectioned under variable angles. At the periphery of those villi there are sinusoid blood capillaries sectioned longitudinally. The capillary wall is tangent to the syncytial membrane (Figure 1). Numerous nuclei belonging to syncytiotrophoblast are condensed at the periphery and near the sinusoid capillaries (Figure 1B, C). In some places there are syncytial sprouts (Figure 1B-D). Frequently, we noticed that the extremities of mature intermediate villi expand to the inter villous space by syncytial buds. When examining with the x40 objective, the syncytial buds are crossed along their central axis by a mesenchyme band that determine compartments. The sinusoid capillaries fully occupy those compartments (Figure 1B – E, I).

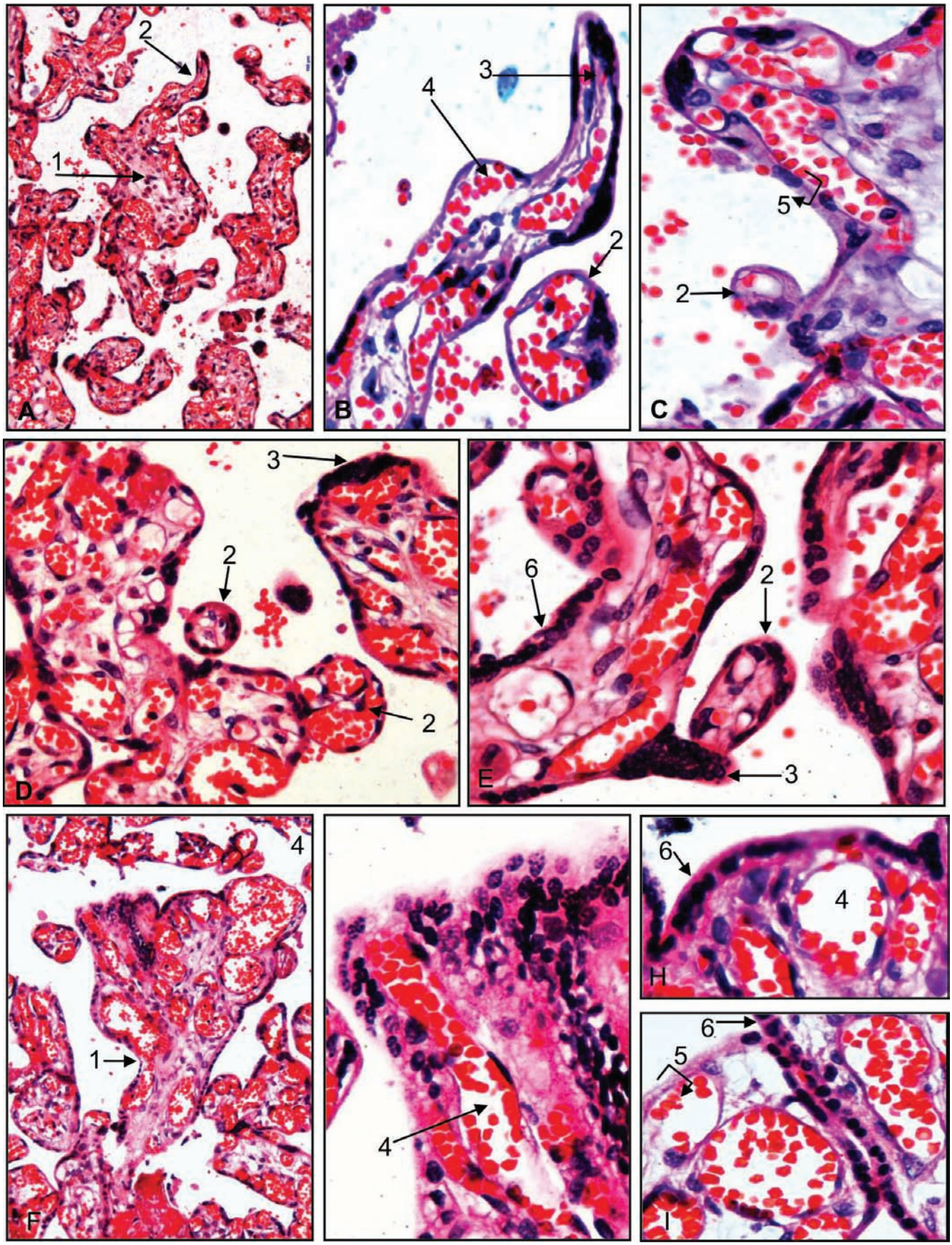

Figure 1. Human placenta after 28 weeks of gestation. The stereo distribution and relations of the foetal sinusoid capillaries to the mature intermediate villi stroma. 1. Mature intermediate villi; 2. Terminal villi; 3. Syncytial knots; 4. Dilated sinusoid capillaries; 5. Vasculosyncytial membrane; 6. Syncytiotrophoblast.
Parafin section. Hematoxiline Eosine stain. x 70 (F); x 140 (A,D) ; x 280 (B,C,E, G–I).

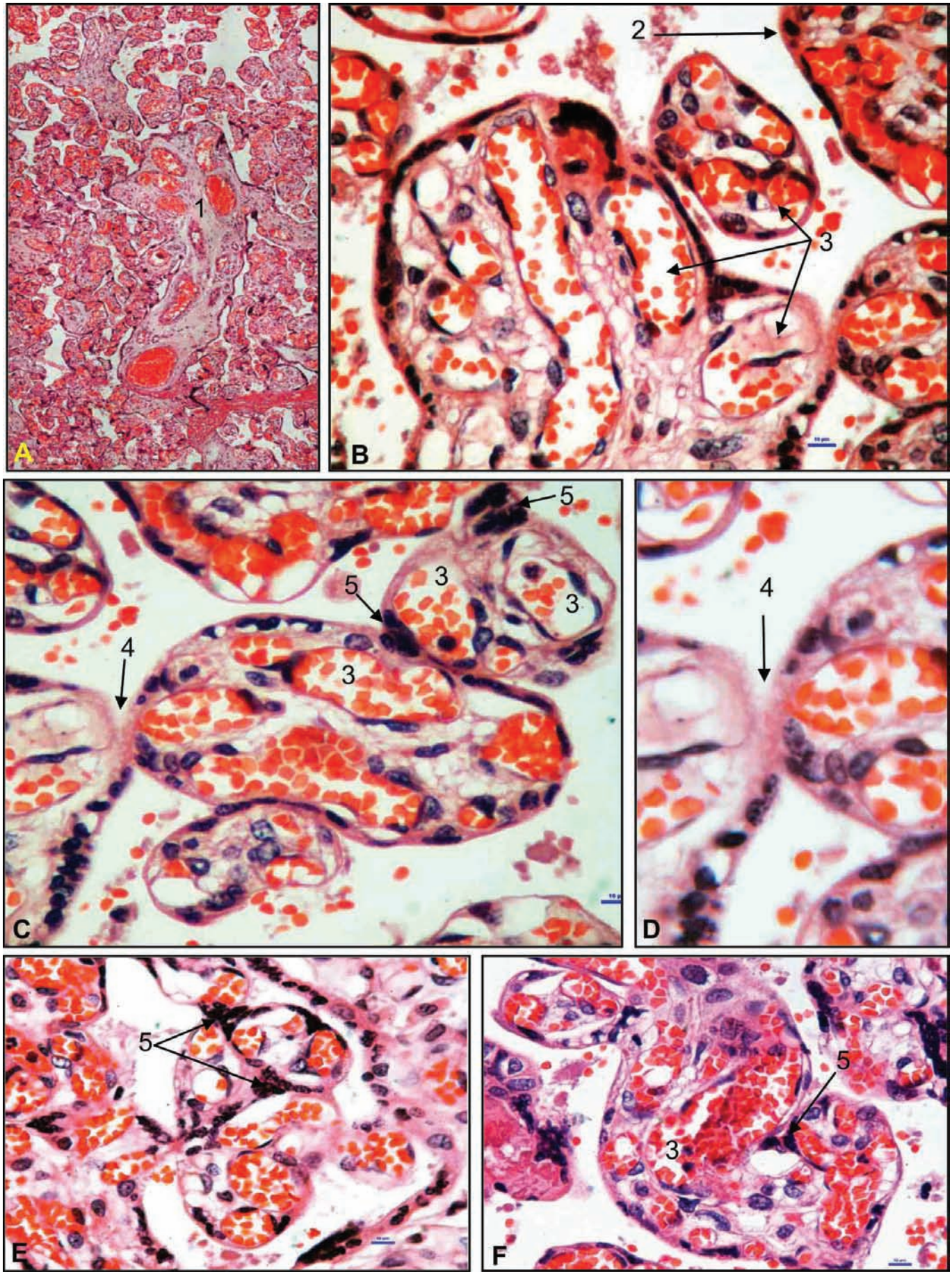

Figure 2. Human placenta after 30 weeks of gestation. The variability of shape of the foetal sinusoid on sections through terminal villi. 1. Stem villi; 2. Terminal villi; 3. Fetal sinusoid; 4. Syncytial bridges; 5. Syncytial knotting.
Parafin section. Hematoxiline Eosine stain. x 140 (A); x 280 (B,C,E,F); x 441 (D).

The contour of mature intermediate villi is serrated on placentas with 30 weeks of gestation; the serrations are determined by mesenchyme and vascular prominent structures covered by a layer of syncytiotrophoblast (Figure 2 A). When examining with the 40x objective we easily observed the discontinuity of syncytiotrophoblast caused by nuclei densification as nuclear aggregates. The terminal villi are in contiguity relations to mature intermediate villi. At that level we pointed out the absence of syncytiotrophoblast (Figure 2 B) and the existence of contiguity relations between the periphery vasculosyncytial membranes (Figure 2 C, D). The central mesenchyme inside mature intermediate villi is crossed by sinusoid capillaries located either central either at the periphery (Figure 2 B, C). The sinusoid capillaries located at the periphery take part to the formation of vasculosyncytial membrane (Figure 2 B-D).

The multiplication of sinusoid capillaries due to angiogenesis, imposes their packing inside the terminal villi with the help of villous mesenchyme, thus obtaining vascular bundles (Figure 2 E) or geometric shapes: torus (Figure 2 F), efflorescence (Figure 4 A, C) or sinusoid serrations (Figure 4 D). The villous mesenchyme is present inside the central sector of those geometric shapes ensuring their resistance structure (Figure 4 A-F).

On the serried sections through placentas with 32 weeks of gestation we observed numerous terminal villi at the periphery of mature intermediate villi (Figure 3 A). When examining with the x40 objective it appears that thick bands of mesenchyme occupy the central part of the terminal villi (Figure 3 C). The sinusoid blood capillaries are present at the periphery of those villi where they have contiguity relations to the syncytial membrane (Figure 3 C,G-I). In some places there are secondary buds that present a large base made of agglomerations of trophoblast nuclei (Figure 3 B). The center of those buds is occupied by sinusoid capillaries sectioned transversally (Figure 3 B). At the periphery of the terminal villi in the sectors that lack the syncytiotrophoblast nuclei, the sinusoid capillaries are superficial and are prominent inside the villous space (Figure 3 C).

A placenta of 36 weeks of gestation harvested from a woman with diabetes, we identified in the central part of the stem villi, the presence of arteries transversally sectioned that had fibro-muscular sclerosis (Figure 3 D-F). The lumen of those arteries is narrowed and allows only a small amount of blood to pass. The terminal villi fully occupy the space between the chorial plate and basal plate . They contain sinusoid capillaries in contact with syncytial membrane (Figure 3 G, H, I).

B. Micro anatomic analysis of collagen IV stereo topography

1. The organization of collagen IV fibers inside the villous capillaries networks

The comparative analysis of the serried sections through placentas stained with Hematoxiline Eosine or Gomori argentic impregnation for argentic collagen IV fibers, brings light to the acknowledgement of the formation of reticulin networks inside villi. One can notice that the reticulin collagen IV fibers distribute around the sinusoid blood capillaries of terminal villi and achieve a large mesh reticuline network (Figure 6 B, D, F, H). At the transition sector between the advehent and revehent blood vessels, there are lines of hyper chromatic long nuclei that resemble pre capillary sphincters (Figure 6 E, G). The same phenomenon is equally seen on Hematoxiline Eosine staine sections or after Gomori argentic impregnation (Figure 6 F, H).

2. The spiral stereo distribution of collagen fiber fascicles inside terminal villi hilum

We used the term hilum for the terminal villi in order to emphasize the sector crossed by the advehent and revehent blood vessels to or away from placenta terminal villi.

On the argentic impregnation serried sections we identified the sector occupied by the hilum of the terminal villi as well as the pre villi vascular pedicle that is surrounded by spiral collagen fiber fascicles (Figure 7). After crossing the hilum, the alanto umbilical vessels distribute to a luxuriant capillary network (Figure 7 E-G).

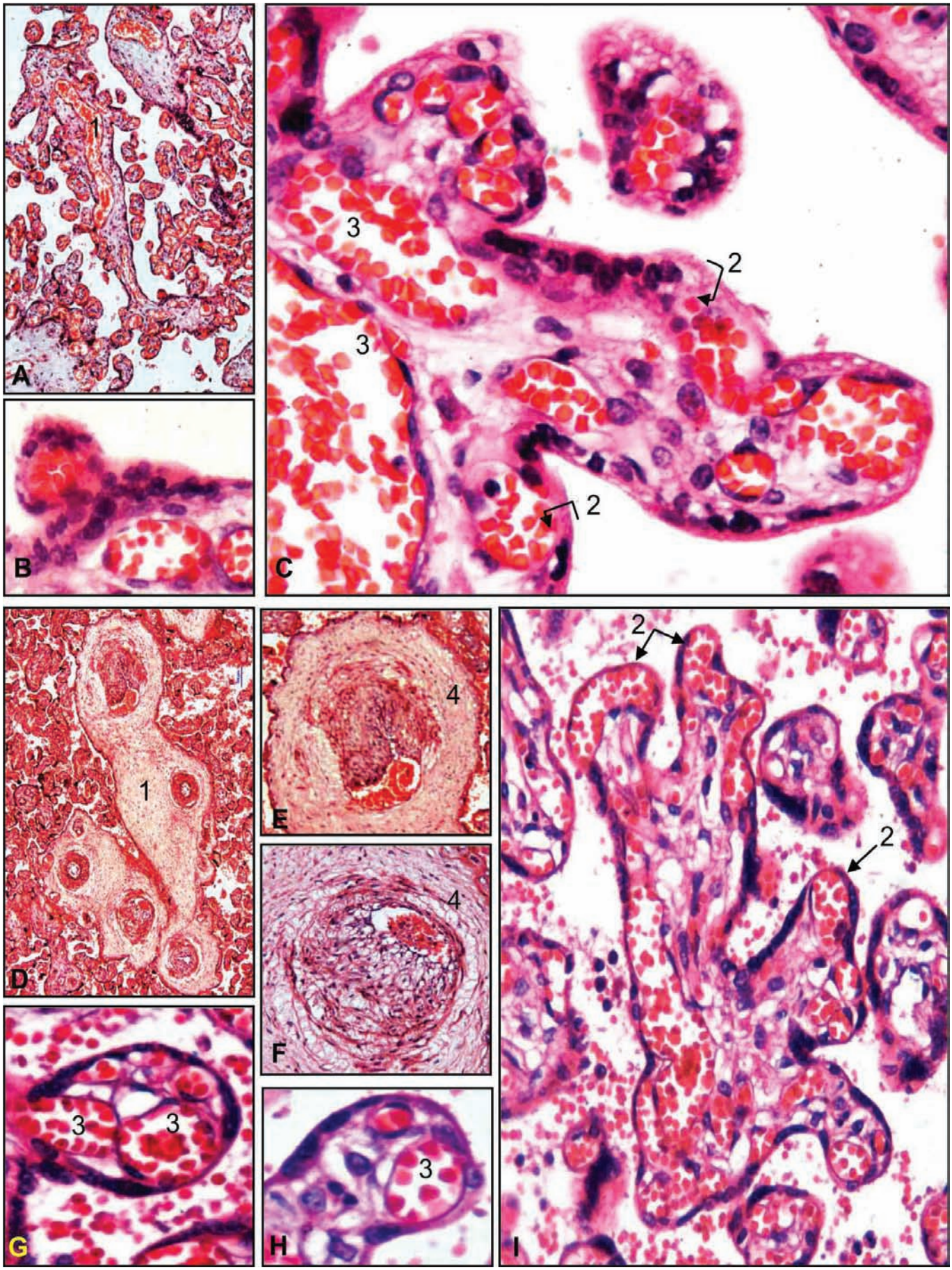

Figure 3. Human placenta after 32 (A-C) and 36 (D-I) weeks of gestation. The stereo topography of terminal villi and vasculosyncytial membrane differentiation. 1. Stem villi; 2. Vasculosyncytial membrane; 3. Fetal sinusoid; 4. Arteries inside stem villi with fiber muscular fibrosis.
Parafin section. Hematoxiline Eosine stain. x 28 (A,D); x 140 (B,E,F,I) ; x 280 (C,G,H).

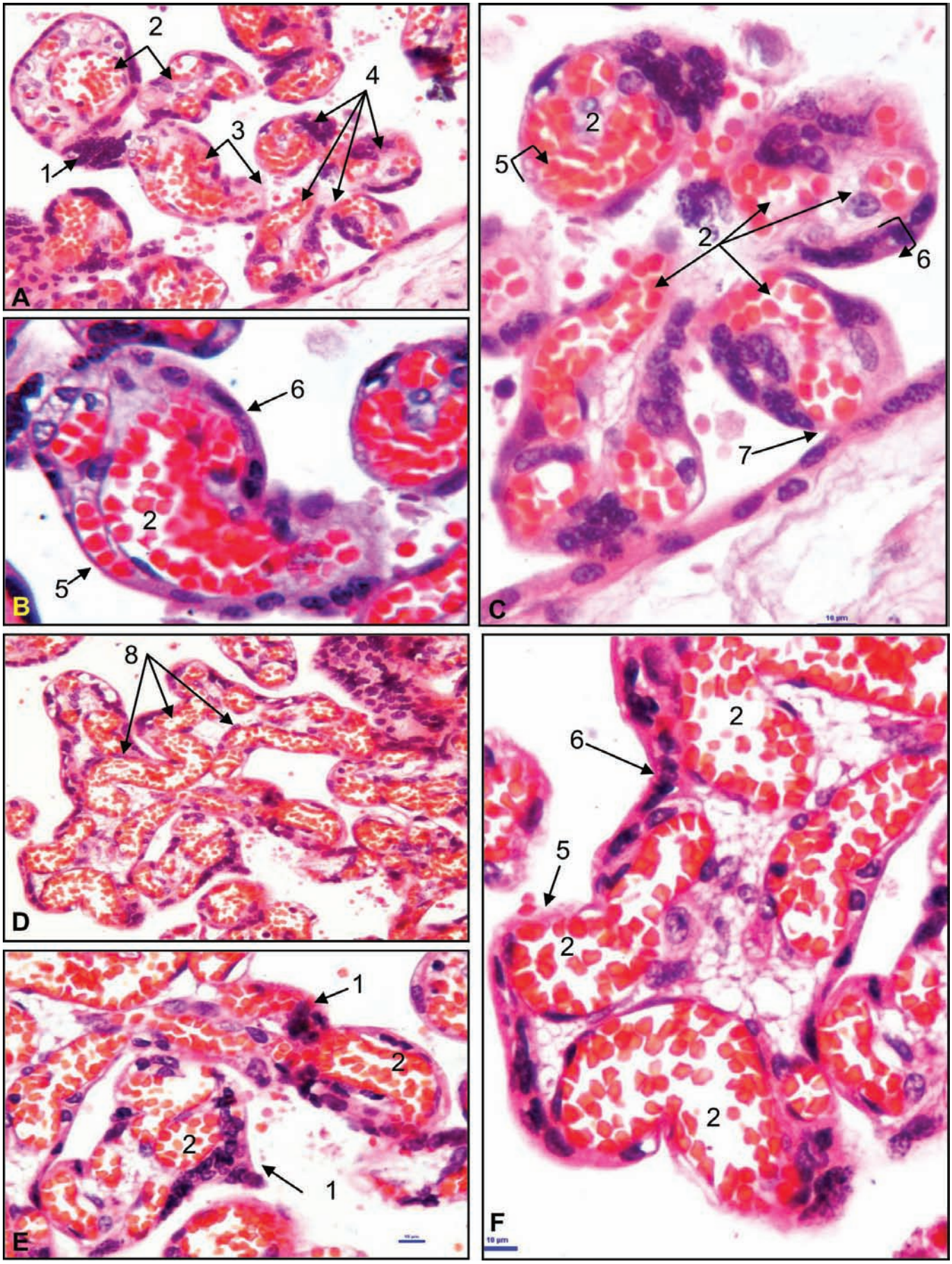

Figure 4. Human placenta after 38 weeks of gestation. The variability of space distribution of the terminal villi. 1. Syncytial knot; 2. Fetal sinusoid; 3. The pedicle of terminal villi; 4. Terminal villi arranged as a bunch of grapes; 5. Vasculosyncytial membrane without trophoblast nuclei; 6. Vasculosyncytial membrane with syncitium; 7. Syncytial bridge; 8. Spiroid fetal capillaries.

Parafin section. Hematoxiline Eosine stain. x 140 (A,D); x 280 (C,E,F) ; x 441 (B).

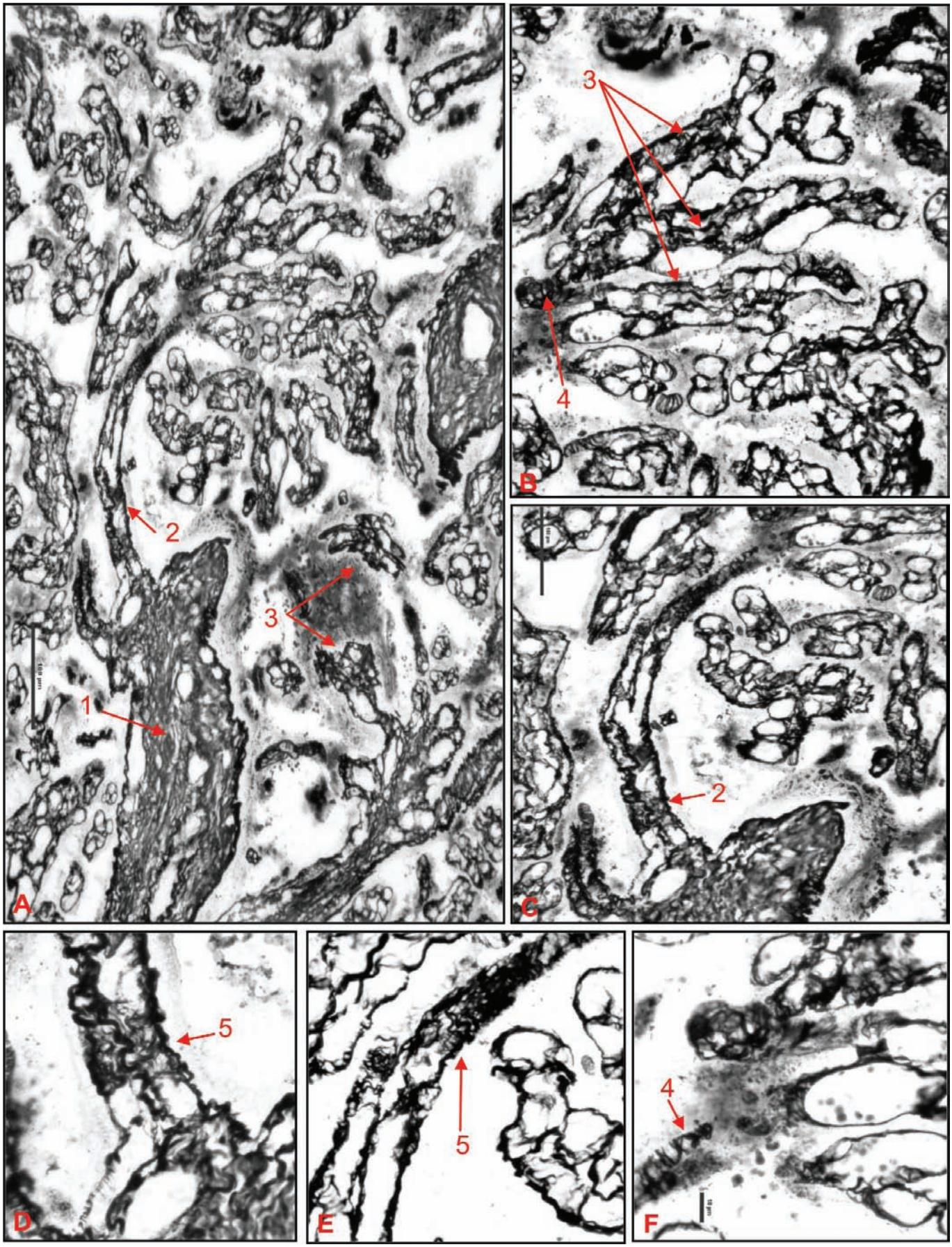

Figure 5. Human placenta after 37 weeks of gestation. The stereo topographic effects of branching angiogenesis evaluated on sections of argentic impregnation as a marker for lamina reticularis inside basal membrane. 1. Stem villi; 2. Mature intermediate villi; 3. Terminal villi; 4. Spiroid collagen fibers inside the vascular pedicle of the terminal villi; 5. Spiroid collagen fibers inside mature intermediate villi.
Parafin section. Gomori argentic impregnation. x 70 (A) ; x 140 (B,C) ; x 280 (D,E,F).

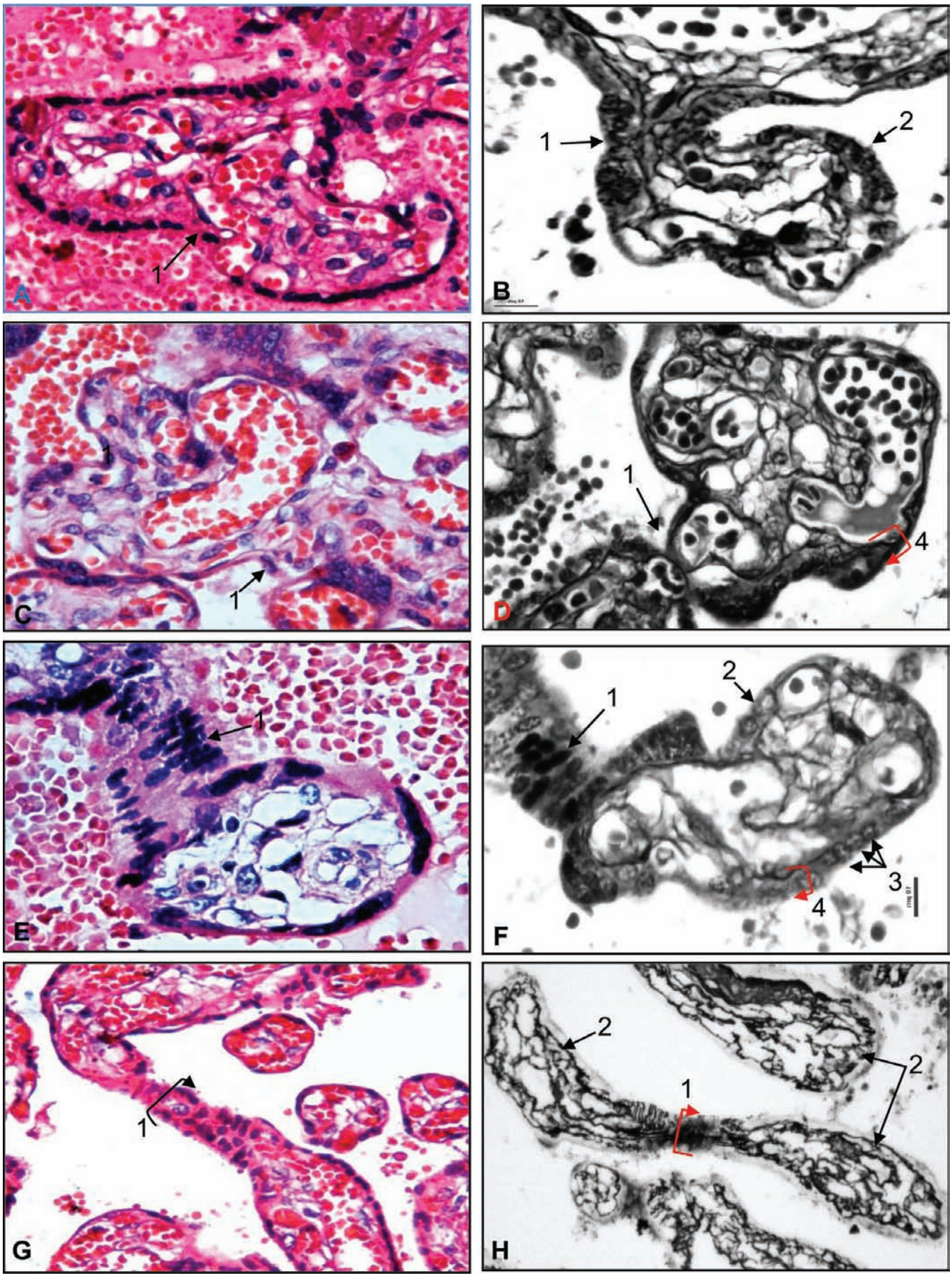

Figure 6. The structural microanatomy of the vascular pedicle of the terminal villi during the third trimester of gestation.
1. Vascular pedicle; 2. Terminal villi; 3. Syncytiotrophoblast; 4. Vasculosyncytial membrane.
Parafin section. Hematoxilin Eosine stain (A, C, E, G). Gomori argentic impregnation (B, D, F, H). x 140 (G.H) ; x 280 (A, C-F) ; x 441 (B).

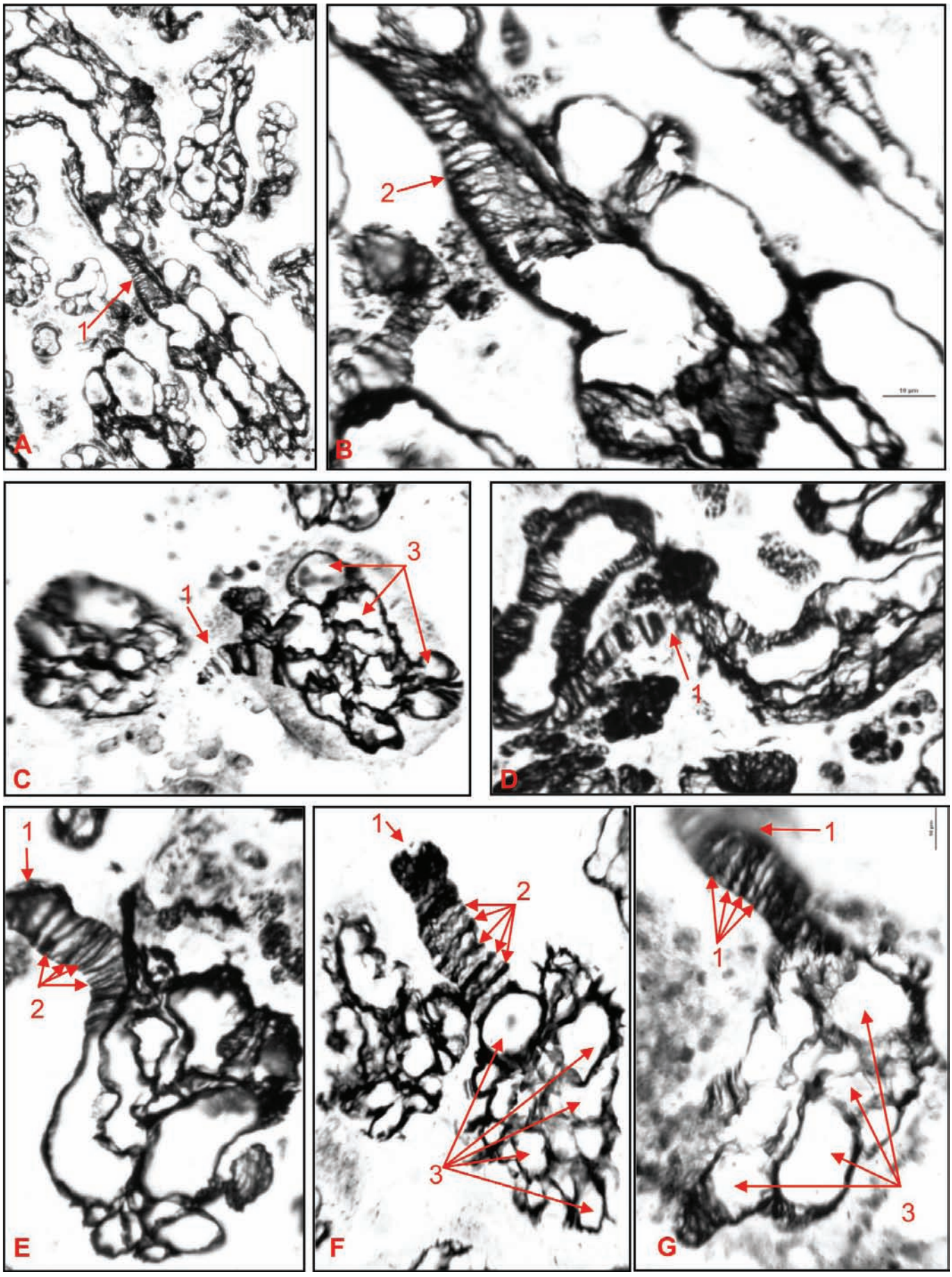

Figure 7. Collagen IV organization and space distribution inside the vascular pedicle of the terminal villi. 1. Vascular pedicle of terminal villi; 2. Spiroid reticulin fiber fascicles inside vascular pedicle; 3. Fetal sinusoid sectioned after variable planes offering an image similar to a bunch of grapes.
Parafin section. Gomori argentic impregnation. x 140(A) ; x 441 (B – G).

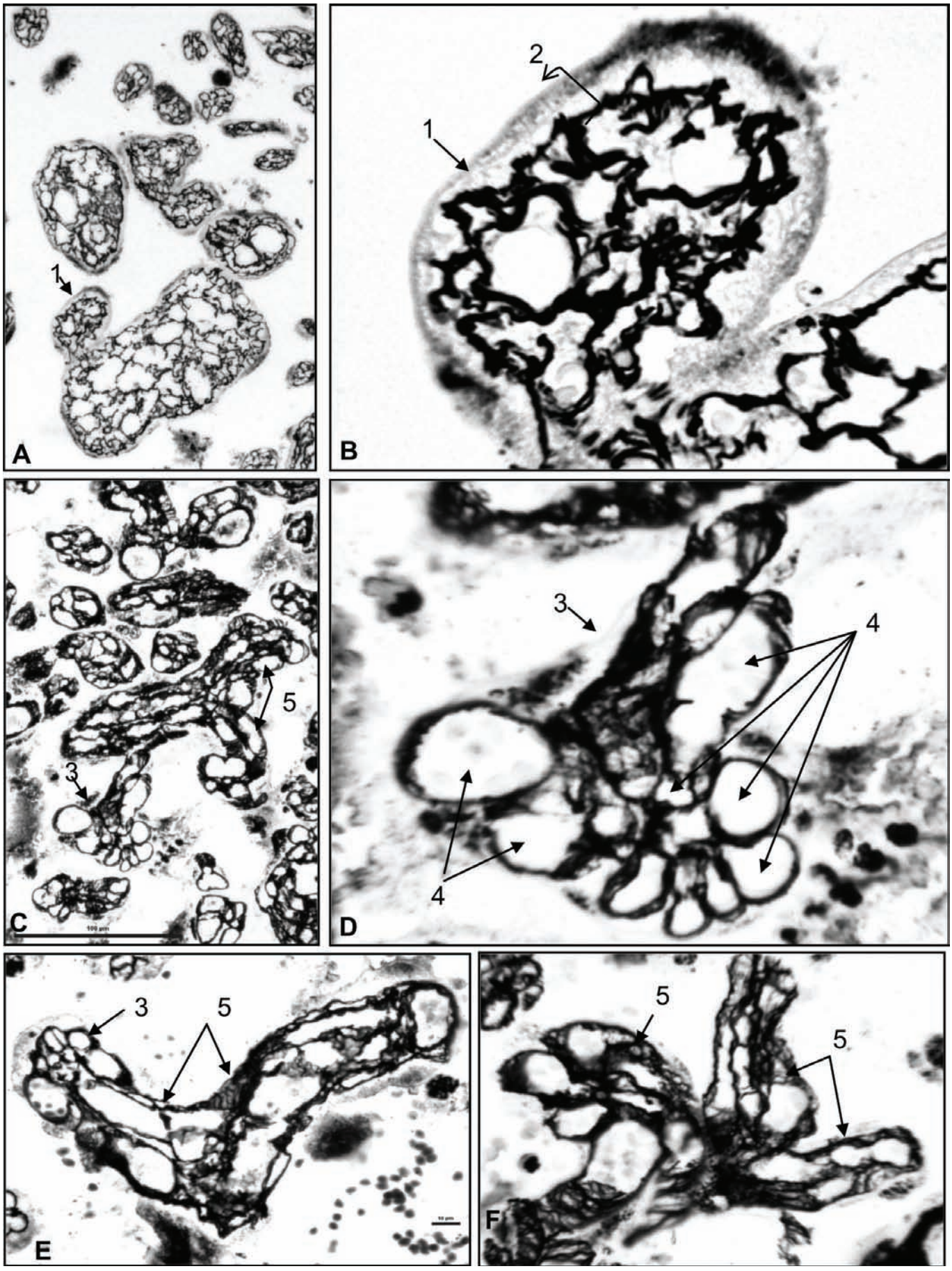

Figure 8. The variability of geometric shapes of the terminal villi during the third trimester of gestation as seen on Gomori argentic impregnation sections. 1. Vascular glomerulus; 2. Vasculosyncytial membrane; 3. Bunch of grapes shape; 4. Fetal capillaries sectioned under variable angles; 5. Branching angiogenesis.
Parafin section. Gomori argentic impregnation. x 70 (A) ; x 140 (C) ; x 280 (E) ; x 441 (B,D,F).

3. Placenta villi phenotype under hypoxia

The evaluation of the villi phenotype was carried out by examining the serried sections of Gomori argentic impregnation through fragments harvested from placentas with 37-38 weeks of gestation. When examining the sections with the x4 objective and the 2D reconstruction images with the x10 objective we saw dichotomy branching of the mature intermediate villi thus obtaining a fan shape image (Figure 5 A). When examining with the x20 and x40 objectives it appeared that the model of multiplication by branching (Figure 5 B; Figure 8 C, E, F) is synchronous with the model of multiplication of blood vessels by non branching (Figure 8 B, D).

Discussions

Micro anatomic phenotype of chorial villi, especially for those during the third trimester of gestation, imposes the acknowledgement of villous functional structures and its genesis, regenesis and remodeling. Three structures are fundamental for the evaluation of the chorial villi phenotype: trophoblast (syncytiotrophoblast and cytotrophoblast); placenta mesenchyme (vascular and angiogenesis); and last but not least the location and relations of type IV collagen.

Trophoblast is implemented inside three structures that can be considered as micro anatomic phenotype markers for chorial villi during the third trimester of gestation: “real sprouting”, “syncytial knots”, “syncytial knoting”.

Placenta mesenchyme generates sinusoid blood capillaries and represents the location for their evolution during gestation dynamics. It contributes to the development of contention structures: atlanto-chorionic parangium and chorio-villous mesangium (Dragoi et al, 2010) [12].

Analyzing our personal observations on the placenta micro structures during the third trimester of gestation, we noticed a significant growth of terminal villi together with intensification in angiogenesis and a reduction in mesenchyme stroma inside mature intermediate villi, an increase in the differentiation of vasculosyncytial membranes, sinusoid capillaries bordering inside terminal villi synchronous with trophoblast structures differentiation: real sprouting and syncytial knots.

Table 1

EVALUATION OF PLACENTA MICROSTRUCTURES DURING THE THIRD TRIMESTER OF GESTATION						
Micro structures		**Weeks of gestation**				
		28	**30**	**32**	**36**	**37**
Trophoblast	**Real sprouting**	+/-	+	+	++	++
	Syncytial knots	-/+	+	+	+	+
	Syncytial knoting	-	+/-	+/-	-/+	-/+
Sinusoid capillary	**Central villi**	++	+/-	+/-	-/+	-/+
	Periphery villi	+/-	++	++	++	++
Mesenchyme stroma		++	+	+/-	+/-	+/-
Vasculosyncytial membrane		-/+	-/+	+	++	++
Angiogenesis	**Branching**	+	+	+/-	+/-	+/-
	Non branching	-/+	+	+	++	++
Villi	**Mature intermediate villi**	++	+	+/-	+/-	+/-
	Terminal villi	+/-	+	++	+++	+++

It is considered that the organization of the villous tree is achieved during two phases: first, the stem and immature intermediate villi are formed and starting from the middle of gestation, there are mature intermediate and terminal villi (Bernirschke and Kaufmann, 2000; Kaufmann et al., 2004) [4, 18]

At the end of gestation, terminal villi reach 10 m2 and have a crucial role for placenta exchanges. The villi growth is influenced by fetal placenta angiogenesis that evolves biphasic together with changes in number and dimensions of vascular segments: capillaries branches during the initial phase followed by non branching angiogenesis (Bernischke and Kauhmann, 2000; MayheW, 2002; Kaufmann et al, 2004) [4, 22, 18].

Human placenta is an organ rich in blood vessels. Placenta vascular network expands and remodels during gestation. It is known that during the first trimester and at the beginning of the second one, the capillary network inside villi increases (Jauniaux et al, 1991; Te Velde et al, 1997) [16, 26] This vascular development is imposed by the oxygen and metabolic demands that are absolutely necessary for fetus growth. It is considered that the integrity of the morph type for trophoblast and fetus capillaries ensures the endocrine and immunologic transport functions of the fetus placenta system. The great majority of the capillary bed is situated inside the terminal branches of the villous tree.

The villous capillaries stereo distribution, the surface and the relations between capillaries and villous trophoblast are very important for the optimal blood dynamics and transport. The formation of terminal villi and its vessels starts during the third trimester and continues until birth (Benirschke et al, 1995) [5] by means of placenta angiogenesis.

There are three stages in the development of placenta blood vessels: vasculogenesis, branching angiogenesis and non branching angiogenesis (Yancopoulos et al, 2000; Carmeliet, 2000) [27, 8]. Vasculogenesis consists of de novo formation of new blood vessels while angiogenesis means formation of capillaries from existing vessels.

The development of the placenta vascular network needs a remarkable coordination between different factors – growth factors specific for the endothelial vascular cells (Charnock-Jones et al, 2000; Ong S. et al, 2000; Ahmed et al, 2000) [9, 23, 1].

Three growth factors play major roles in vasculogenesis and branching or non branching angionesis during gestation:

VEGF-A – induces vasculogenesis and angiogenesis;

Ang 1 – leads to maturation of the vascular network;

Ang 2 – destroys vascular networks.

Vascular endothelial growth factor VEGF-A has mitotic potential, is a survival factor for endothelial cells at the initiation of angiogenesis and vasculogenesis by the induction of endothelial cells proliferation, and by migration and sprouting. VEGF plays an essential role in the formation of new blood vessels (Frater et al, 2008; Helske et al, 2001) [14, 15]

During gestation, VEGF participates to the trophoblast proliferation, migration and metabolic activation (Shiraishi et al, 1996). Ang 1 and Ang 2 act in sequence during the late stages of angiogenesis together with VEGF-A (Yancopoulos et al, 2000; Carmeliet, 2008) [27, 8].

Jirkovska et al (2001) [17] described two ways for capillaries development: longitudinal growth and branching. Inside terminal villi the villous capillary bed is achieved by longitudinal growth and not by capillary branching.

The micro anatomic analysis of the transition sector between mature intermediate villi and terminal villi allowed for the evaluation of the spiral collagen fiber fascicles stereo distribution inside vascular pedicle of terminal villi. Those aspects draw attention to the existence of flow regulating structures at that level.

There were not identified pre capillary sphincters or segments cushioned by a muscle layer (Rhodin, 1967) [24]. It is considered that the terminal part of arteries continues directly to one or more capillaries by gradually reducing the diameter and smooth muscle layer loss (Kaufmann et al, 1985; Leiser et al, 1991) [19, 20].

The terminal villi development depends on capillaries growth (Kaufmann et al, 1985). Sinusoid capillaries are characteristic for mature placenta and are not comparable to sinusoid capillaries from liver, spleen or bone marrow. They are different from conventional cinusoid capillaries as they have larger diameters and appear as vascular dilatations (Kaufmann, 1985) [19]. The functional signification of placenta sinusoid capillaries caused many speculations. The location of many sinusoid capillaries close to the villous extremity, sustains Arts's conclusion (1961) [3] that the sinusoids locally decrease the blood flow favoring the fetus mother exchanges.

The basal membrane of sinusoid capillary and trophoblast basal membrane establish contiguity relations and achieve the vasculosyncytial membrane identified by Bremer in 1916 [6]and defined later by Amstutz (1960) [2].

In preeclampsie, pregnant women placentas that gave birth to a hypotrophic and/or premature fetus, presents changes in blood vessels network (Zhon et al, 1997) [28]. Precocious hypoxia in preeclampsie can be followed by a compensatory villous growth that allows for a normal blood circulation inside villi vessels. Chronic ischemia and hypoxia can lead to a decrease in number of terminal villi and an increase of dilatation concerning sinusoid capillaries (Macara et al, 1996) [21].

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