

Histology of Human Placenta

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ABSTRACT

The placenta is a key organ for pregnancy evolution and fetal growth. Placental anatomic abnormalities may affect the placental functions, interfering in turn with maternal and or fetal wellbeing. This chapter describes the placental development, the macroscopic aspect and the histological characteristics through the gestation. The aim of this chapter is to provide updated information to help clinicians to distinguish between normal or abnormal placenta, to improve understanding of pregnancy outcome pathophysiology.

INTRODUCTION

The placenta is the fetal organ that acts on maternal-fetal exchanges of gas and nutrients, fetal waste removal, and immunological and endocrine function, supporting pregnancy. It develops after conception, at the time of implantation of the blastocyst in the uterus, and is generally discharged from the uterus following infant birth.

PLACENTAL DEVELOPMENT

After conception the fertilized oocyte migrates through the fallopian tube and it establishes in the uterine cavity. The pregnancy begins and the fertilized oocyte undergoes next developmental stages. Between the developmental stage of the morula and blastocyst, a specialized cell line, termed the trophoblast, begins to differentiate. At around 4 days post conception, the cells composing the morula (called blastomers) begin to secrete a fluid that accumulates in the morula forming the blastocyst cavity. At this stage, an inner compact cell mass forms the embryoblast, whereas an outer mononuclear layer of cells forms the trophoblast that surrounds the blastocyst cavity. Approximately 6-7 days after conception the blastocyst attaches to the uterine decidua and the formation of the placenta begins [1,2].

The trophoblastic tissue covering the outer side of the inner mass, the so-called polar trophoblast (Figure 1A), represents the blastocyst tissue that adheres, attaches and implants into the uterine wall. After the attachment to the uterine decidua, the polar trophoblast undergoes the next differentiation step, forming the syncytiotrophoblast by syncytial fusion of mononucleated cells. The syncytiotrophoblast exhibits an invasive ability, which allows its penetration into the decidua. This step is fundamental for achieving complete implantation of the conceptus in the decidua and the covering of the blastocyst by decidual stroma (Figure 1B). The syncytiotrophoblast faces the decidua and represents a mantle that surrounds the blastocyst [1]. At this time, a second line of mononucleated cells forms: the cytotrophoblast, located directly below the syncytiotrophoblast. The cytotrophoblast undergoes rapid division and fusion with the syncytiotrophoblast. Hence, the cytotrophoblast permits the expansion of the syncytiotrophoblast [1,3].

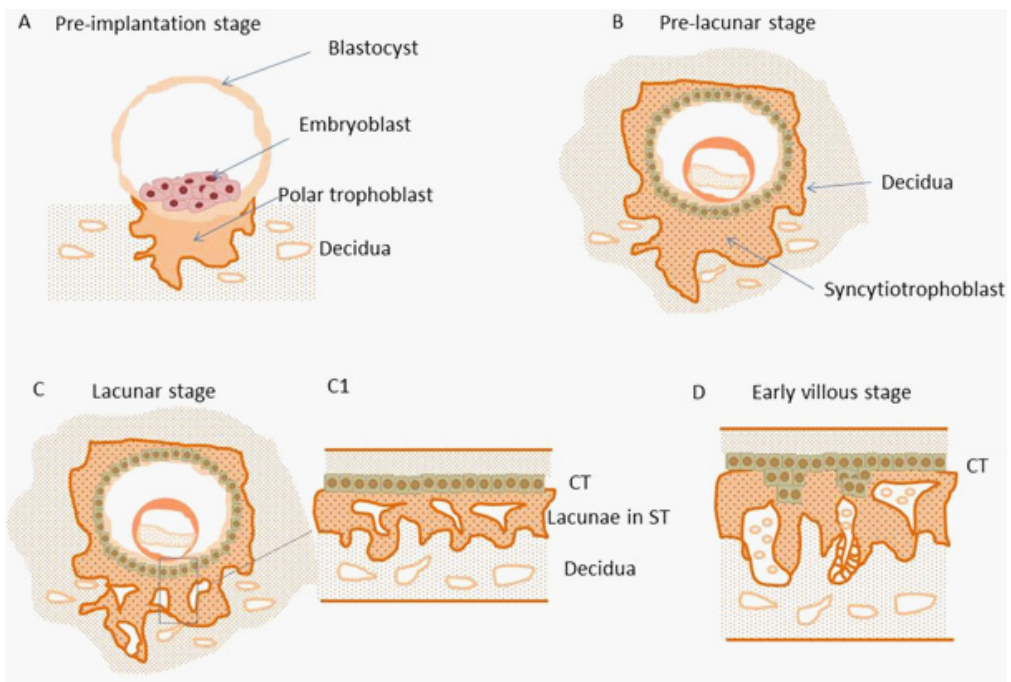


Figure 1: Cartoons representing the early stages of development of the human placenta.

- A. The blastocyst hatches from the zona pellucida and attaches to uterine decidua. The attachment of the blastocyst to the uterus occurs thanks to the polar trophoblast.
- B. During the prelacunar stage the polar trophoblast undergoes a differentiation step to generate the first oligonucleated syncytiotrophoblast (ST).
- C. During the lacunar stage, irregular spaces called lacunae appear in the syncytiotrophoblast. These lacunae are filled with fluids originated from uterine secretions.
- D. Thanks to its lytic activity through the decidua, the syncytiotrophoblast reaches and erodes the maternal the capillaries permitting the advent of few maternal blood cells in the lacunae. In the syncytiotrophoblast a core of cytotrophoblast (CT) develops and the primary villi begin their formation.

Around eight days after conception, irregular spaces called lacunae (Figure 1C), appear in the syncytiotrophoblast. These lacunae are filled with fluids that originate from uterine secretions, and join to form the precursor of the intervillous space. The remaining syncytiotrophoblast forms the basis of the placental villous tree. Hence, three fundamental areas of the placenta are detectable: the early chorionic plate facing the embryo; the lacunar system involved in the development of the intervillous space and the villous tree; and the primitive basal plate facing the maternal decidua [1].

Thanks to its lytic activity through the decidua, the syncytiotrophoblast reaches and erodes the maternal capillaries, permitting the advent of a small number of maternal blood cells in the lacunae (Figure 1D). This represents the precursor of primitive maternal circulation in the placenta [1].

At about 12-13 days following conception, cytotrophoblast cells penetrate into the syncytiotrophoblast, creating the primary trophoblast villi that protrude into the intervillous space (Figure 2).

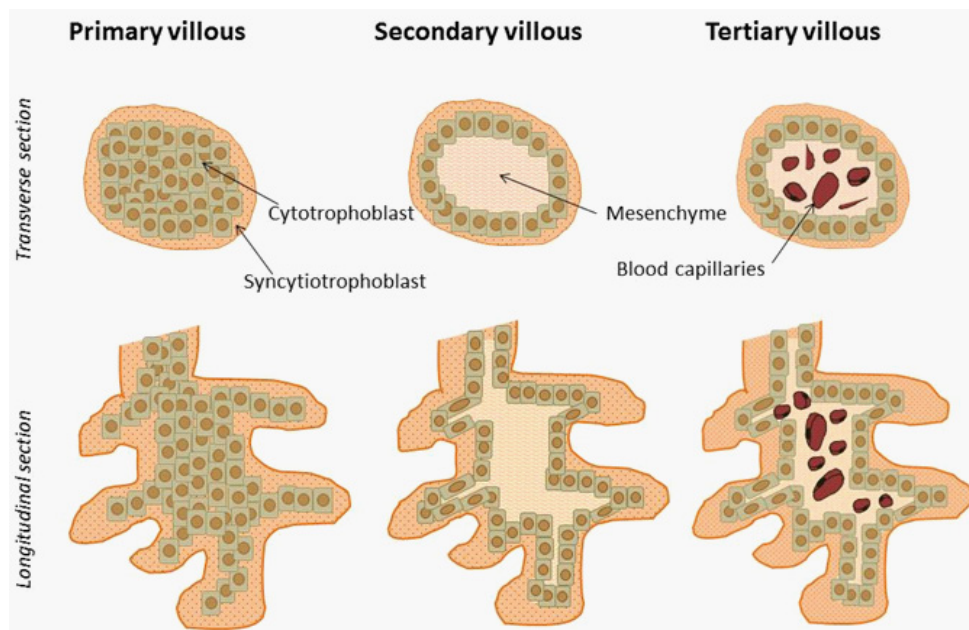


Figure 2: Development of the first trimester placental villi.

Primary trophoblast villi develop when cytotrophoblast cells penetrate into syncytiotrophoblast. When the extra-embryonic mesoblast penetrates into the primary villi, a mesenchymal core is created transforming the primary villi in secondary villi. Tertiary villi develop when the hematopoietic cells develop within the mesoblast.

After day 15, some of these villi contain a pool of cytotrophoblastic cells that invade the syncytiotrophoblast, reaching maternal tissues and forming the cytotrophoblastic anchoring columns (Figure 3). Following this, some cytotrophoblastic cells leave the villi and differentiate into the extravillous trophoblast, a specialized type of cells with an invasive phenotype. These cells then invade the maternal decidua, reaching the maternal spiral arteries, and erode the wall of the vessel, transforming the spiral arteries into low resistance tubes with continuous flow (Figure 3). With this step, maternal circulation begins.

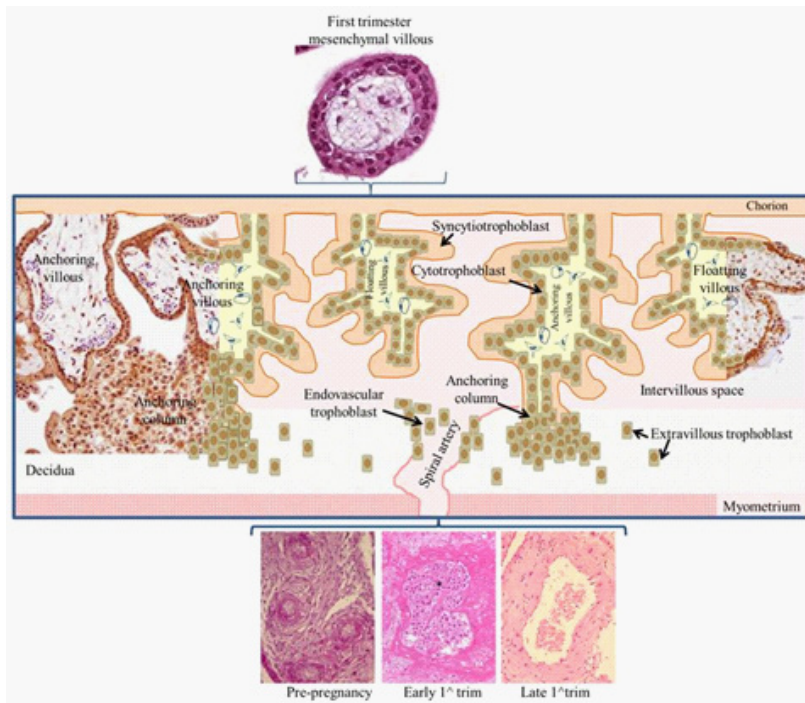


Figure 3: Early human placenta.

Cartoon shows the differences between the floating villi and the anchoring villi: note the cytotrophoblastic cells that have trespass the syncytiotrophoblast reaching maternal tissues and forming the cytotrophoblastic anchoring columns; a pool of cytotrophoblastic cells have leave the villi and differentiate into the extravillous trophoblast, as well as some cytotrophoblastic cells have an invasive phenotype by which have reached the maternal spiral arteries forming the endovascular trophoblast.

The histological images at bottom show the aspect of the spiral arteries through the pregnancy, from the typical arterial aspect before the onset of the gestation (muscularized wall), to the aspect during the early first trimester during which the vessel has been invaded by the endovascular trophoblast forming the trophoblastic plug (asterisk), to the final aspect of the vessel with the total loss of the muscular wall.

The upper histological image shows the typical aspect of first trimester mesenchymal villous, with loose stroma surrounded by two trophoblastic layers, the cytotrophoblast (the inner layer) and the syncytiotrophoblast (the outer layer).

At about 16 days following conception, the extra-embryonic mesoblast penetrates into the primary villi, forming a mesenchymal core that transforms the primary villi into secondary villi (Figure 2).

A few days later, hematopoietic cells develop within the mesoblast, creating the tertiary villi (Figure 2) and the precursor of fetal circulation in the placenta.

At the end of the early developing stage, a placental villous is formed from the inner to the outer site, by a fetal capillary endothelium, a loose connective tissue surrounding the fetal villous vessels, a cytotrophoblastic villous layer and a syncytiotrophoblastic villous layer. These four elements together float as a placental villous into the maternal blood that wets the intervillous space and forming the placental barrier (Figure 4) through which maternal-fetal exchanges occur.

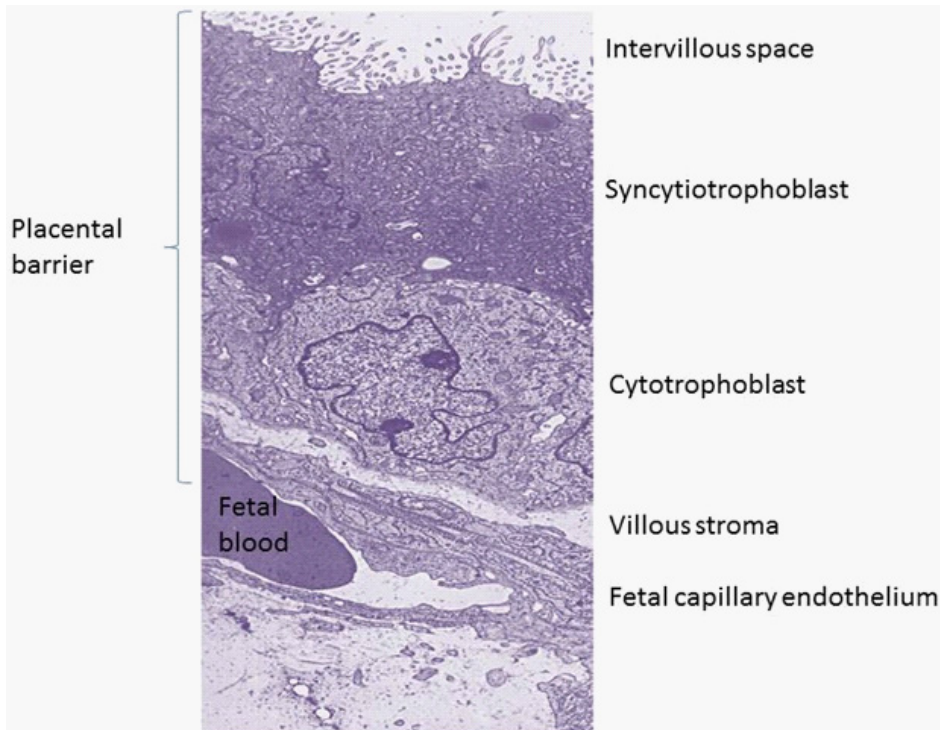


Figure 4: The placental barrier.

Maternal-fetal exchanges occur through the placental barrier, a multilayer anatomical site that has been showed in this transmission electron microscopy image. From the inner to the outer site, the placental barrier includes the fetal capillary endothelium, the connective tissue that surrounds the fetal villous vessels, the cytotrophoblast and the syncytiotrophoblast. These four elements compose the placental villi. Placental villi float into the maternal blood that wets the intervillous space. Maternal-fetal exchange occurs between the maternal blood of the intervillous space and the fetal blood of the villous capillaries through the layer of the placental barrier.

Note the characteristic aspect of the brush border of the syncytiotrophoblast. This surface of maternal site of the syncytiotrophoblasts is named microvillous membrane.

(Modified from [16]).

THE PLACENTAL VILLOUS TREE

Throughout the progression of the pregnancy, the villous cytotrophoblast gradually disappears from the internal site of the walls of the tertiary mesenchymal villi, and the structure of the villi changes, to reduce the distance between the maternal blood located in the intervillous space and the fetal vessels contained in the villous stroma. This process improves maternal-fetal exchanges. At the end of the pregnancy, five types of villi form the placenta: mesenchymal villi, immature intermediate villi, stem villi, mature intermediate villi and terminal villi.

Mesenchymal Villi

Mesenchymal villi are the most primitive type of villi, developed during the early stages of pregnancy [4,5]. Mesenchymal villi measure 100-250 μm in diameter [1] and exhibit weakly organized loose stroma, containing mesenchymal cells (Figure 5). During the first trimester of pregnancy, the stroma is surrounded by two trophoblastic layers – the cytotrophoblast (inner layer) and the syncytiotrophoblast (outer layer). Throughout the progression of the pregnancy, the cytotrophoblastic layer gradually disappears. Therefore in the third trimester of pregnancy mesenchymal villi exhibit a continuous layer of syncytiotrophoblast with sporadic internal “islets” of cytotrophoblast. Fetal capillaries of mesenchymal villi are poorly developed. Until six weeks of gestation, mesenchymal villi represent the only type of villous developed in the placenta. They are therefore very important during the early weeks of pregnancy for endocrine activity and the proliferation of the other types of villi [5]. At full-term of gestation their volume is less than 10% of total villi [5].

Immature Intermediate Villi

Immature intermediate villi are large (100-400 μm in diameter), bulbous villi (Figure 5) developed following differentiation of mesenchymal villi [1]. This type of villi exhibits a characteristic stroma containing a reticular structure formed by matrix-free channels parallel to villi long axis [1]. These stromal channels contain numerous placental macrophages called Hofbauer cells. Arterioles, venules and capillaries in the villous stroma are very small; the cytotrophoblastic layer is discontinuous whereas the outer syncytiotrophoblastic layer remains thick and continuous. Immature intermediate villi are considered the principal sites of maternal-fetal exchanges from 8 to 22 weeks of gestation [1,5,6].

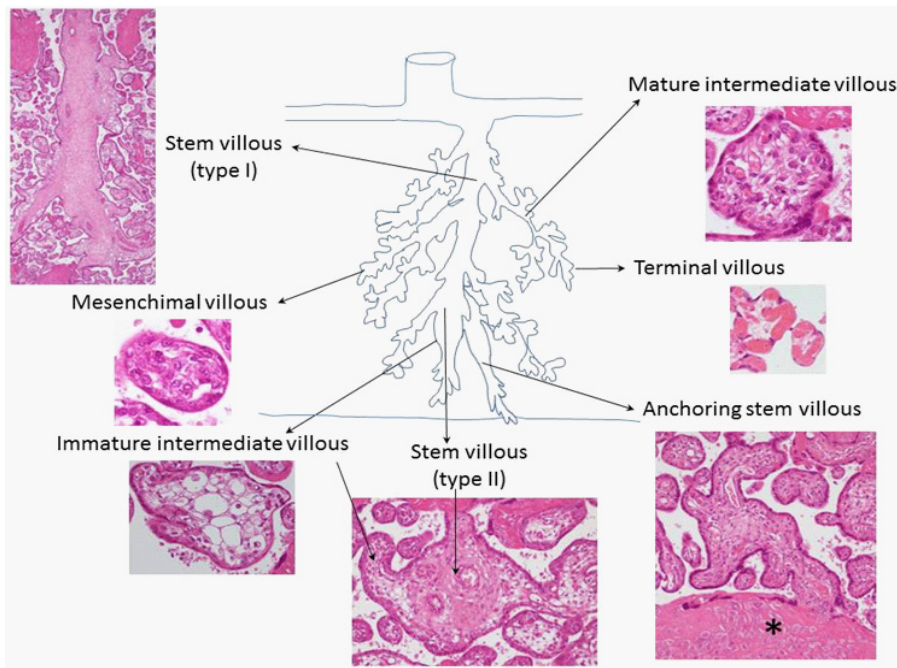


Figure 5: Types of placental villi forming the placental villous tree.

Stem villi are the largest villi in the placental villous tree; types I include stem villi with a caliber more than 250 μm . Stem villi type II comprises stem villi with a caliber of 120-300 μm . Mesenchymal villi are rich in mesenchymal cells and poor in capillaries. Immature Intermediate villi show the characteristic stromal channels containing Hofbauer cells. Mature Intermediate villi have loose stroma containing small peripheral vessels and capillaries. Terminal villi show the highly dilated sinusoids and the thin vasculo-syncytial membrane.

* = decidua

Stem Villi

Stem villi provide the mechanical stability of the villous tree [1,5,6]. They are the largest villi of the placenta with a diameter of 100-3000 μm [1]. Stem villi derive from the differentiation of the immature intermediate villi, and are characterized by a condensed fibrous stroma containing central arteries and veins with a thick smooth muscle wall (Figure 5). Because of their histological characteristics (as the low degree of fetal capillary), stem villi contribute minimally to the fetal-maternal exchange and to the placental endocrine activity [1,5].

Mature Intermediate Villi

Mature intermediate villi are long, slender villi differentiated from mid-gestation from peripheral ramifications of the stem villi [7]. They are 80-150 μm in diameter and consist of a loose

stroma containing small peripheral vessels and capillaries [1] (Figure 5). Thanks to their intense fetal vascularization, mature intermediate villi are considered the first important structure for fetal-maternal exchanges [5].

Terminal Villi

Terminal villi are grape-like structures developed from mature intermediate villi [1,7,8]. They are the final branches of the placental villous tree [1]. They measure 30-80 μm in diameter and 100 μm in length [1,9] and are characterized by a high degree of capillarization and highly dilated sinusoids (Figure 5). The fetal capillaries of the terminal villi face a very thin syncytiotrophoblastic layer forming the vasculo-syncytial membranes, the most important site for physiological fetal-maternal exchanges [1,5]. In the normal full-term placenta, the terminal villi represent approximately 40% of the villous volume of the placental villous tree [5].

In summary, from the early primitive villous a step-by-step harboring structure develops, forming the placental villous tree: a stem villous divides into 3-5 mature intermediate villi, which further branches into 10–12 terminal villi [5]. In a full-term placenta, 60–70 harboring structures (or fetal lobules) arise from the chorionic plate [1]. The vast majorities of villi float freely in the intervillous space and intervene in the fetal-maternal exchange, whereas others are attached to the decidua, providing structural stability for the placenta. Villi characteristics composing the placental villous tree are summarized in table 1.

Table 1: Histological characteristics of the placental villi.

Type of villous	Diameter (μm)	Stroma	Vessels	Time of comparison	Percentage at full-term
Mesenchymal villi	100-250	Loosely arranged collagen fibers enmeshing mesenchymal and some Hofbauer cells	Poorly developed	Early first trimester	1
Immature intermediate villi	100-400	Reticular structure with numerous fluid-filled channels containing macrophages (Hofbauer cells)	Small arterioles, venules located between the stromal channels	Mid-first trimester (8 weeks of gestation)	0-5
Stem villi	100-3000	Condensed, fibrous, containing collagen fibers, occasional fibroblast and rare macrophages	Muscularized arteries and veins in the center of the villous	Mid-first trimester (8 weeks of gestation)	20-25
Mature intermediate villi	80-150	Loose bundles of connective tissues fibers, fixed connective tissue cells	Peripheral numerous capillaries, small terminal arterioles and collecting venules	Mid-gestation	25
Terminal villi	30-80	Absent	High degree of sinusoidal capillarization, involving more than 35% of the villous volume	Late second trimester-early third trimester	40-45

MACROSCOPIC ANATOMY OF THE PLACENTA

The full-term human placenta is a circular disc-shaped organ which diameters measure about 20 and 22 cm, with a central thickness of 2.5 cm. Although many factors influence the weight of the term placenta (such as the mode of delivery, the time at which the umbilical cord is clamped, and the time between the delivery of the placenta and the weighing), an average placental weight is about 470 g [1].

Observing the gross structures of the delivered placental, two surfaces can be identified: the fetal site (corresponding to the chorionic plate, the inner site of the primitive polar trophoblast) and the maternal site (corresponding to the basal plate, the site by which the primitive polar trophoblast adheres to the maternal decidua) (Figure 6).

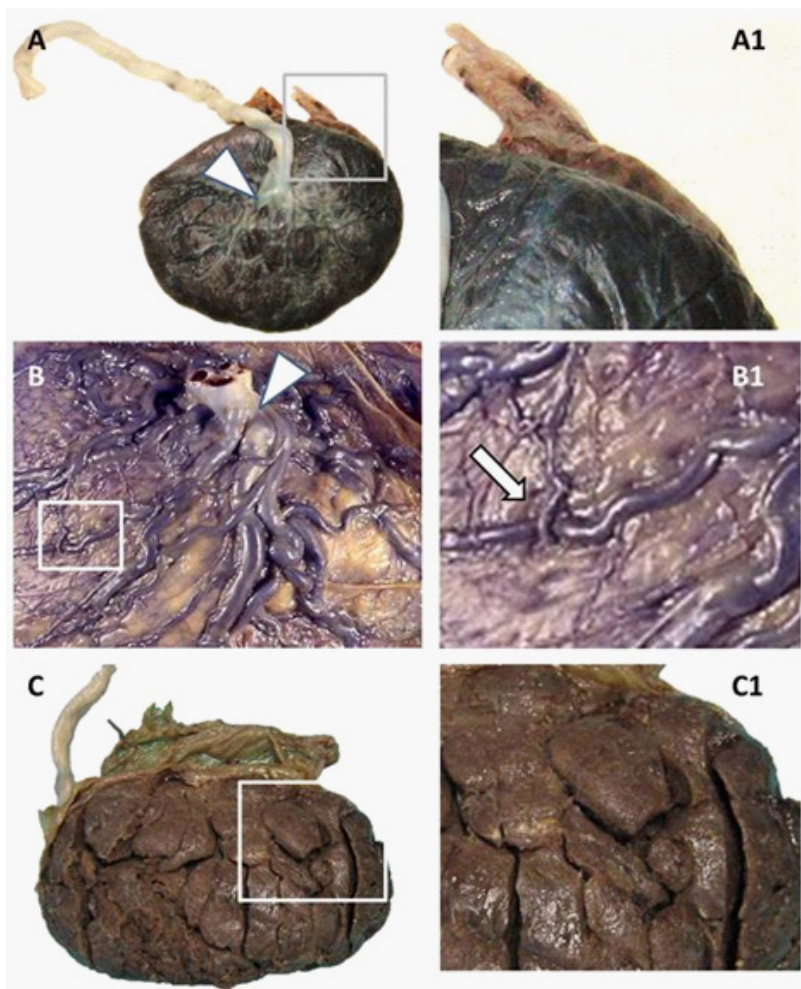


Figure 6: Macroscopic aspect of the delivered human placenta.

A: fetal surface of the placenta. Note the site of cord insertion (arrow head). A1: high power image of the placental border with the insertion of the amniotic membranes.

B: distribution of the chorionic vessels in the fetal placental surface from the site of cord insertion (arrow head). B1: high power image of the chorionic vessels with the cross between an artery (upper) and a vein (under) (arrow).

C: maternal surface of the placenta. Note the subdivision of the surface in numerous maternal cotyledons. C1: high power image of the maternal cotyledons.

Fetal Surface of the Placenta

The fetal surface of the placenta contains the chorionic plate [1]. This structure is covered by the amnion, a single layered epithelium and by the amniotic mesenchyme, an avascular connective tissue. These tissues form the amniotic sac, the bag in which the fetus develops and lives during the intrauterine life (Figure 7).



Figure 7: Macroscopic aspect of the anatomic localization and interrelationship between fetus, amniotic sac and placenta.

The umbilical cord inserts (Figure 6) in a central, or near-central position of the chorionic plate, and carries the fetal blood from the fetal body to the placenta and vice versa. The chorionic plate mesenchyme contains the chorionic vessels, ramifications of vessels originating from the umbilical cord (Figure 6). From the two fetal umbilical arteries, the chorionic arteries branch in the chorionic plate in a centrifugal pattern, forming their final branches that supply blood to the villous tree [1]. The chorionic veins are direct continuations of the veins of the villous tree, that give rise to the single umbilical vein [1]. Usually, in the surface of the chorionic plate, the chorionic veins cross the chorionic arteries underneath [1] (Figure 6).

Maternal Surface of the Placenta

The maternal surface of the placenta, termed the basal plate, is an artificial, shallow structure that originates from the separation of the placenta from the uterine wall at the end of delivery. The basal plate is a mixture of fetal extravillous trophoblasts and uterine decidua, often accompanied with fibrinoid and blood clots [1].

The surface of the basal plate is incised by the placental septa, which form deep clefts that subdivide the basal plate into 10–30 regions called maternal lobes or cotyledons. Histologically, each maternal lobe is occupied by one to four fetal lobules [10].

A perpendicular section of the placental disc shows all the aforementioned structures, including the chorionic plate, the villous tree and the basal plate (Figure 8).

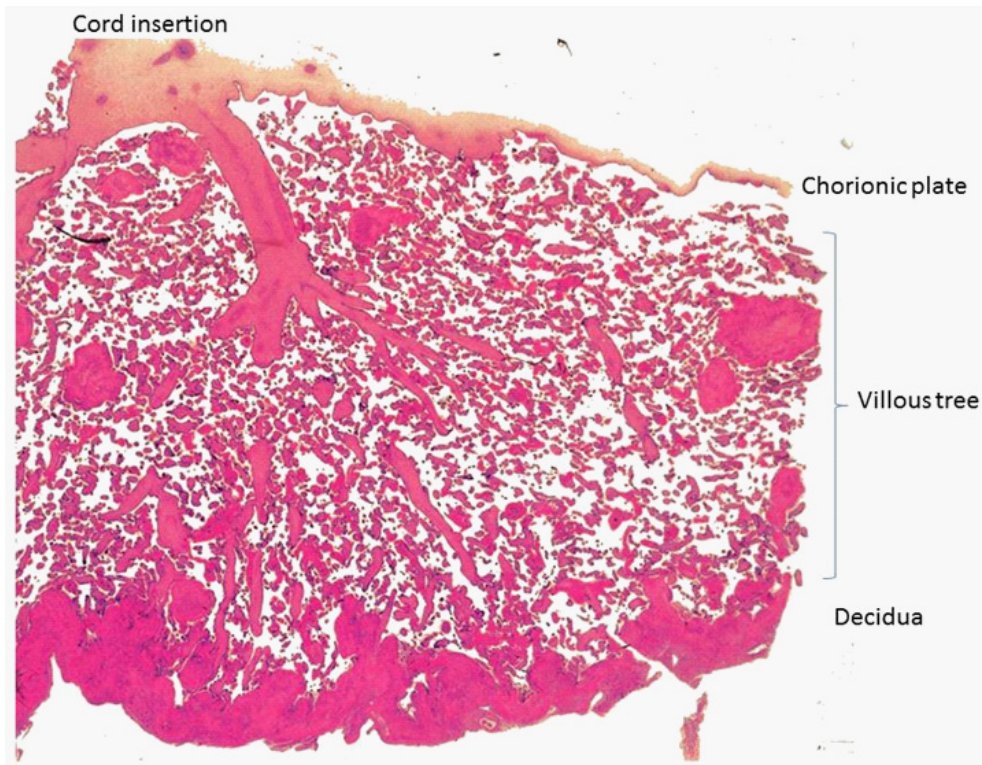


Figure 8: Full-thickness section of human placenta.

At the placental margin, the maternal and fetal surfaces join; the chorionic and basal plates merge and form the smooth chorion; and the fetal membranes or the chorion leave [1]. The chorion laeve includes three layers: the amnion with its epithelium and mesenchyme; the chorion with a layer of mesenchyme and a layer of extravillous trophoblast; and the decidua capsularis [1].

After birth, placental characteristics should be observed by an extensive evaluation, examining for potential abnormalities that can affect neonatal wellbeing as previously reported [11]. An example of the macroscopic features that should be evaluated in the delivered placenta is shown in Table 2.

Table 2: Example of macroscopic features evaluable in the delivered human placenta and that have to be recorded in the clinical-pathological report.

Macroscopic evaluation of the delivered placenta

Placental Membranes

- Site of rupture: imprecise; precise (cm of distance from the placental margin);
- Insertion: normal; marginal; circummarginate/circumvallate;
- Features: thick; thin; opaque; shiny; meconium stained;
- Presence of abnormalities: retromembranous hemorrhage; edema.

Umbilical cord

- Length (cm);
- Maximum and minimum diameter (site and cm);
- Coiling (number of twists);
- Site of insertion in the placental disk: central; marginal; velamentous;
- Features: color; eventual presence of true knots (number and distance from the site of cord's placental insertion); false knots; stricture (number, length, diameter); aneurism; hematoma (number and size); gross evidence of thrombosis; cysts (diameter); rupture (site and length).

Placenta disk

- **General evaluation of placental disk**
 - Placenta weight (without umbilical cord and membranes);
 - Placental diameters (cm × cm);
 - Placental thickness: maximum (cm); minimum (cm);
 - Placental shape: round; ovoid; irregular;
 - Eventual presence of accessory lobes (number and diameter; presence of interconnection between multiple lobes by velamentous vessel).
- **Evaluation of the fetal surface**
 - Color (opaque; shiny; green due to meconium deposition);
 - Other superficial characteristics (amnion nodosum; cyst);
 - Characteristics of the chorionic vessel (distribution of the vessels; presence of vascular anastomosis; presence of anomalies such as thrombosis, hemorrhage, masses).
- **Evaluation of the maternal surface**
 - Macroscopic aspect: integral; disrupted; presence of prominent cotyledon; compressed area (with or without hematoma);
 - Evaluation of eventual lesions: hematoma (site and size); infarcts (number and diameter; % of the placenta involved; temporal characteristics of the infarct zone: fresh, early or old infarct), marginal sclerosis; calcification; fibrin deposition;
 - Other lesions.

Examples of abnormalities

Abnormal membrane insertion

Abnormal cord insertion

Abnormal fetal surface

Abnormal maternal surface

THE ROLE OF THE PLACENTAL HISTOLOGY IN THE CLINICAL PRACTICE

As exposed two centuries ago ‘a diseased fetus without its placenta is an imperfect specimen, and a description of a fetal malady, unless accompanied by a notice of the placental condition, is incomplete. Deductions drawn from such a case cannot be considered as conclusive, for in the missing placenta or cord may have existed the cause of the disease and death. During intrauterine life the fetus, the membranes, the cord and the placenta form an organic whole, and disease of any part must react upon and affect the others’ [12].

Modern medicine is confident that this affirmation is true. The placental histology can add useful information in ascertaining the cause and mechanism involved in adverse pregnancy outcomes [13]. Although an interpretation of histological lesions is complex, and requires skill and insight into clinical-pathologic correlation [13], histological placental evaluation provides valuable features that are useful to parents in understanding the cause of an adverse outcome [11,14,15,16,17], and useful to health care providers both for parent counseling and as a legal defense in cases of medical malpractice allegations [13]. Indeed, the vast majority of obstetric litigations are related to unskilled evaluation of the placenta. In some cases this results from a failure to identify the clinical importance of placental lesions. In others a failure to detail clinical significance of observed placental lesions in medical records. In other cases there is a failure to communicate to the parents these cause-and-effect relationships [18]. An extensive placental evaluation and a skilled clinic-pathological interpretation should always be performed in the clinic to improve the comprehension of the physiopathology of the normal or adverse pregnancy outcome.

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References

1. Huppertz B. The anatomy of the normal placenta. *J Clin Pathol*. 2008; 61: 1296-1302.
2. Aplin JD. The cell biological basis of human implantation. *Baillieres Best Pract Res Clin Obstet Gynaecol*. 2000; 14: 757-764.
3. Pötgens AJ, Schmitz U, Bose P, Versmold A, Kaufmann P. Mechanisms of syncytial fusion: a review. *Placenta*. 2002; 23: 107-113.
4. Castellucci M, Scheper M, Scheffen I, Celona A, Kaufmann P. The development of the human placental villous tree. *Anat Embryol (Berl)*. 1990; 181: 117-128.
5. Wang Y, Zhao S. Chapter 3, Structure of the Placenta. *Vascular Biology of the Placenta*. San Rafael (CA): Morgan & Claypool Life Sciences; 2010.
6. Castellucci M, Kaufmann P. Chapter 7. Architecture of normal villous trees. *Pathology of the human placenta*. 5th Edition. Ed: Benirschke K, Kaufmann P, Baergen R. 2006; 121–173.
7. Kaufmann P. Development and differentiation of the human placental villous tree. *Bibl Anat*. 1982; 29-39.
8. Kaufmann P, Sen DK, Schweikhart G. Classification of human placental villi. 1. Histology. *Cell Tissue Res* 1979; 200: 409–423.
9. Boyd JD, Hamilton WJ. *The human placenta*. Cambridge: Heffer and Sons, 1970.
10. Kaufmann P. Basic morphology of the fetal and maternal circuits in the human placenta. *Contrib Gynecol Obstet*. 1985; 13: 5-17.

11. Avagliano L, Marconi AM, Candiani M, Barbera A, Bulfamante G. Thrombosis of the umbilical vessels revisited. An observational study of 317 consecutive autopsies at a single institution. *Human Pathology*. 2010; 41: 971–979
12. Ballantyne JW. Diseases and deformities of the foetus. Oliver and Boyd. Edinburgh. UK
13. Baergen RN. The placenta as witness. *Clin Perinatol*. 2007; 34: 393-407.
14. Avagliano L, Bulfamante GP, Morabito A, Marconi AM. Abnormal spiral artery remodelling in the decidual segment during pregnancy: from histology to clinical correlation. *J ClinPathol* 2011; 64: 1064-1068
15. Avagliano L, Marconi AM, Romagnoli S, Bulfamante GP. Abnormal spiral arteries modification in stillbirths: the role of maternal prepregnancy body mass index. *J Matern Fetal Neonatal Med*. 2012; 25: 2789-2792.
16. Avagliano L, Terraneo L, Virgili E, Martinelli C, Doi P. Autophagy in Normal and Abnormal Early Human Pregnancies. *Reprod Sci*. 2015; 22: 838-844.
17. Avagliano L, Locatelli A, Danti L, Felis S, Mecacci M, Bulfamante GP. Placental histology in clinically unexpected severe fetal acidemia at term. *Early Human Development*. 2015; 91: 339–343.
18. Kraus FT. Perinatal pathology, the placenta and litigation. *Hum Pathol*. 2003; 34: 517-521..