
Pathology of the Placenta: A Continuum Spectrum of Inflammation from Physiology to Disease

4

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Contents

4.1	Introduction.....	49
4.2	Natural Killer Cells.....	50
4.3	Macrophages.....	52
4.3.1	Decidual Macrophages.....	52
4.3.2	Placental Macrophages.....	52
4.4	T Cells.....	53
4.4.1	T Regulatory Cells.....	53
4.5	Dendritic Cells.....	55
4.6	B Cells.....	55
4.7	Trophoblast as Regulator of Innate Immune Cell.....	56
4.8	The Alteration of the Maternal–Fetal Equilibrium of the Inflammatory Cells.....	56
4.8.1	Acute Chorioamnionitis.....	56
4.8.2	Chronic Chorioamnionitis.....	59
4.8.3	Chronic Villitis of Unknown Etiology.....	59
4.8.4	Chronic Villitis in Oocyte Donation.....	59
4.8.5	Chronic Deciduitis.....	60
4.9	Inflammatory Lesions of the Decidua.....	62
	References.....	62

4.1 Introduction

Pregnancy is a biologic example of a successful semi-allogenic graft: at the fetomaternal interface, the semi-allogenic embryonic cells that adhere and “dig” into the decidua are protected from maternal immune rejection. The fetomaternal interface is localized between the maternal uterine mucosa and the trophoblastic cells [1].

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Maternal decidua does not represent a passive tissue in which blastocyst implants and develops its placenta. Maternal tissues not only do not reject trophoblastic cells but play an active role to support the placental development and function: the endometrium undergoes a specialized tissue reaction called decidualization whereby cell morphology, cell activity, gene expression, and immune cell distribution contribute to support the blastocyst apposition, adhesion, and implantation within the decidua [2].

The placenta originates from the extraembryonic portion of the polar zone of the blastocyst that adheres to the uterus during the implantation process. From the adhesion process of the blastocyst to the uterine decidua, the trophoblastic tissue undergoes a series of differentiations to develop into its final aspect of villi composed of stromal tissue containing fetal vessels and surrounded by trophoblastic cells: cytotrophoblast and syncytiotrophoblast, the inner and outer villous trophoblastic layers, respectively [3]. Meanwhile, a specific type of villi, called anchoring villi, permits to anchor the placenta to the decidua, by means of cytotrophoblast cells, named trophoblastic anchoring columns. Some of these trophoblastic cells detach from the columns and migrate through the decidual stroma, reach the spiral arteries, penetrate the wall of the maternal vessels, and colonize the lumen of the spiral arteries. This ignites the complex and essential process of vascular remodeling of spiral arteries. Maternal inflammatory cells now start to work against their natural mission and tolerate and accept this invasion of these extravillous, semi-allogenic, trophoblastic cells.

A cross talk between trophoblast and decidua is a fundamental prerequisite to maintain maternal immune tolerance toward the semi-allogenic embryo and to allow trophoblast invasion, placental development, and pregnancy evolution. This cross talk includes the expression of immune cells, dynamically dependent on the pregnancy progression [4]:

- The first trimester of pregnancy is a phase of physiological inflammation [5]: leucocytes not only tolerate pregnancy but also they support gestation [6]. Immune cells in the first trimester are mainly natural killer (NK) cells (about 70 %) and macrophages (about 20 %), whereas the number of T cells is variable (about 10–20 %) and dendritic cells, B cells, and regulatory T cells are rare [7] (Fig. 4.1).
- The second trimester of pregnancy is a phase of predominant anti-inflammatory state. In this time frame, the mother and fetus are in symbiosis and the fetus undergoes rapid development and growth [5].
- The late third trimester of pregnancy is a phase characterized by a reversion to a pro-inflammatory condition that characterizes human parturition of an altricial newborn [5].

4.2 Natural Killer Cells

In pregnancy, decidual natural killer cells have a characteristic and specific phenotype (CD56^{BRIGHT}, CD16⁻, CD3⁻). They change their structure as pregnancy progresses to adapt themselves to the role of pregnancy supporters.

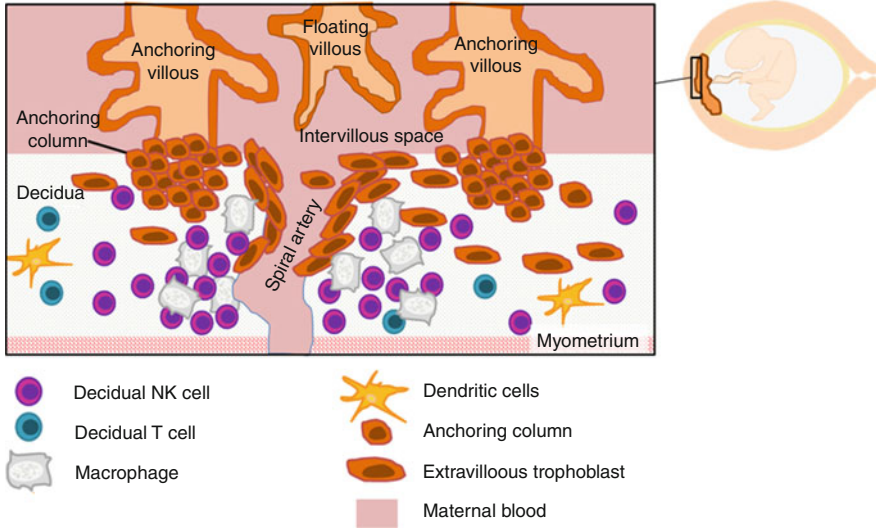


Fig. 4.1 Normal distribution of inflammatory cells at the fetomaternal interface. Decidual natural killer and macrophages accumulate near the maternal spiral artery during the remodeling process. The vessel undergoes dramatic anatomic modification, lacking the smooth muscular wall and the elastic fibers and transforming in a low-pressure, high-conductance vessel. Inflammatory cells play a role in the removal of dying cells and cellular debris, to facilitate trophoblast migration and invasion. Moreover, inflammatory cells contribute to maternal tolerance versus the semi-allograft conceptus. Extravillous trophoblasts invade into the decidua from the anchoring villi and progressively replace the endothelium of the vessel. This type of extravillous trophoblast takes the name of “endovascular trophoblast,” and it is directly in contact with the maternal circulation. To avoid maternal reject reaction, extravillous trophoblast expresses a nonclassical major histocompatibility complex class I: it expresses a specific type of human leukocyte antigen (HLA), the HLA-G. HLA-G enters the maternal circulation and binds with the leukocyte immunoglobulin-like receptor on decidual natural killer cells, macrophages, and T lymphocytes, inactivating leukocytes and, in turn, inducing tolerance

During the first trimester, NK cells contain specific granules rich in angiogenic growth factor and vascular endothelial growth factor C. Moreover, during the first stage of pregnancy, decidual NK cells secrete matrix metalloproteinases MMP2 and MMP9. These enzymes break down the extracellular matrix. This process directly helps trophoblast migration and invasion. At this stage, NK cells play a decisive role for the proper placental development, promoting spiral artery remodeling. The number and the function of uterine NK cells are crucial for the physiological evolution of pregnancy. Their abnormalities have been associated with implantation failure [8], miscarriage [9], preeclampsia, and fetal growth restriction [10].

In the second trimester, decidual NK cells undergo a degranulation process. This will stop the production of angiogenic and vascular growth factors. Interferon- γ (INF- γ) secretion starts to oppose vascular development. During the third trimester, the uterine NK cells in the decidua are degranulated. In this stage, their production of INF- γ inhibits the trophoblastic invasiveness, protecting the uterus from a too deep trophoblastic migration [6].

4.3 Macrophages

At the feto-maternal interface, macrophages represent the second most abundant leukocyte population within the human decidua. Commonly, macrophages are classified in two different types: M1, the proinflammatory type, and M2, the immune-regulatory type [11]. The type of decidual macrophages appears to be predominantly M2 [12]. Their function is that of immune suppression, scavenging of apoptotic cells, clearing cellular debris, and promoting tissue remodeling.

4.3.1 Decidual Macrophages

Decidual macrophages are maternal cells and protect human pregnancy throughout gestation by inhibiting the immune response by decidual NK, T lymphocytes, and other circulatory macrophages [6]. Thanks to their additional production of matrix metalloproteinases 9 and vascular endothelial growth factor, decidual macrophages are believed to play a role in the spiral artery remodeling [12]. Despite this role in spiral artery modification, the association between abnormal number or function of decidual macrophages and preeclampsia is controversial [7].

4.3.2 Placental Macrophages

Placental macrophages, also called “Hofbauer cells,” are CD68⁺ fetal cells early detectable in pregnancy in the villous stroma. Since Hofbauer cells appear in the placental villi prior to the appearance of the fetal circulation, they may originate in the early stage of pregnancy from progenitor cells within the population of mesenchymal cells in the villous stroma; then, later in pregnancy, they may originate from penetration of embryonic bone marrow-derived monocytes into the villous stroma [3]. Generally, macrophages intervene in phagocytosis of apoptotic bodies and cellular debris as well as antigen presentation in response to inflammation and infectious insults; the specific role of placental macrophages has not been fully understood yet [13]. Their close contact with endothelial progenitor cells and primitive vessels suggests that Hofbauer cells intervene in early placental vascular genesis [14]. Moreover, the identification of proteins regulating branching morphogenesis localized to Hofbauer cells permits to hypothesize a role of placental macrophages in the development of the placental villous tree [15]. Alterations in the number and aspect of Hofbauer cells may be associated with complications of pregnancy such as fetal immune or nonimmune hydrops and fetal metabolic storage diseases such as GM1 gangliosidosis, glucuronidase deficiency, and type VII mucopolysaccharidosis [13]. Histological features of elevated concentration of Hofbauer cells have been related to adverse pregnancy outcome in association with villitis of unknown etiology or acute chorioamnionitis (see below) [13].

4.4 T Cells

T cells are poorly represented within the human decidua. Their role is not completely understood.

During the early stages of pregnancy, a successful implantation occurs in a finely regulated pro-inflammatory/anti-inflammatory microenvironment; T cells seem to play a crucial role in this balance. T-helper (Th) cells can be classified into Th1 cells, which are involved in cellular immunity, and Th2 cells, which are involved in humoral immunity [16]. In the past, maternal tolerance of the semi-allogenic graft was explained by an absolute predominance of the Th2-type immunity, which overrules Th1-type immunity, therefore protecting the fetus from maternal Th1-cell attack [17]. More recently, the role of Th1 has been reconsidered, showing that Th1 activity plays an important role in pregnancy, promoting Th2 response, regulating the placentation process, defending the maternal–fetal microenvironment against infections, and later cooperating in the initiation of delivery [18]; therefore, the concept of absolute Th2 predominance has been reconsidered and the hypothesis of “Th1–Th2 cooperation” has been introduced [18]. Moreover, it has been suggested that differences in the expression of the Th1 pro-inflammatory action and Th2 anti-inflammatory action depend on the phase of pregnancy: early and late pregnancy needs a Th1 milieu, whereas Th2 cells prevail in mid gestation (Table 4.1) [5]. Abnormal pregnancy outcome may occur in the presence of an aberrant Th1/Th2 profile: an excessive Th1 reaction may be associated with recurrent miscarriage, preterm delivery, and preeclampsia [18, 19], but even an increase of Th2 secretion at the feto-maternal interface could be associated with miscarriage and preeclampsia [18].

Histological features of placental elevated concentration of T cells have been associated with adverse pregnancy outcome as may occur in chronic deciduitis, chronic chorioamnionitis, and villitis of unknown etiology [7] (see below).

4.4.1 T Regulatory Cells

T regulatory cells (Treg) are a subset of T lymphocytes that act as strong suppressors of inflammatory immune response with a fundamental role in preventing destructive immune response and auto-inflammatory and autoimmune disease, warranting peripheral self-tolerance and immune homeostasis [20, 21]. Treg cells levels are high in maternal blood during the first and second trimesters of pregnancy and decline prior to delivery and postpartum [20]. Moreover, Treg cells physiologically accumulate in the maternal decidua. A deficiency in Treg cells number has been associated with recurrent miscarriage and preeclampsia [20]. Indeed, it is of interest to underline that there are two developmental pathways of Tregs: thymic (tTreg) and extrathymic or peripheral (pTreg). tTregs appear to suppress autoimmunity, whereas pTregs operate to downregulate responses to

Table 4.1 Inflammatory balance in pregnancy

Phase of pregnancy	Predominant immunological features	Physiological events	Comment
Early pregnancy	Th1	Blastocyst apposition to the uterus	In this phase, an inflammatory microenvironment needs for removing of apoptotic cells and cellular debris, for achieving an adequate repair of the uterine epithelium, and for the maternal tolerance versus the semi-allogenic embryo
		Decidual breaking for the blastocyst implantation	
		Trophoblast invasion of the decidua	
		Breaking into the spiral artery and disruption of the smooth muscular wall by the extravillous trophoblast, to warrant an adequate placental–fetal blood supply	
		Trophoblast replacement of the spiral arteries endothelium	
Mild pregnancy	Th2	Placental development	In this phase, an anti-inflammatory status predominates, but the mother maintains her ability to respond against infective–immunological insults
		Fetal growth	
		Fetal organ maturation	
Late pregnancy	Th1	Cervical ripening	In this phase, a recrudescence of an inflammatory status is necessary to promote parturition
		Myometrial contraction	
		Labor and delivery	
		Expulsion of the placenta	
		Uterine involution	

Modified from Mor [17]

antigens, such as those from ingested food, symbiotic bacteria, and allergens. Genomic analysis allowed to hypothesize that pTregs emerged in eutherian (placental) mammals to protect from maternal–fetal conflict. As a matter of fact, conserved noncoding sequence 1 (CNS1), which is required for pTreg development, has been detected present in all placental mammals, whereas it is absent in non-placental mammals such as the wallaby, opossum, and platypus, as it is expected to be absent in non-mammals such as zebra fish. pTregs specifically sort out paternal antigens in the trophoblastic cells and suppress effector T cells in an active process to induce tolerance [22]. Figure 4.2 shows the quasi-perfect correspondence between wild-type pregnant mice and knocked-out ones as regards embryonic reabsorption and number of females that presents reabsorbed embryos [23].

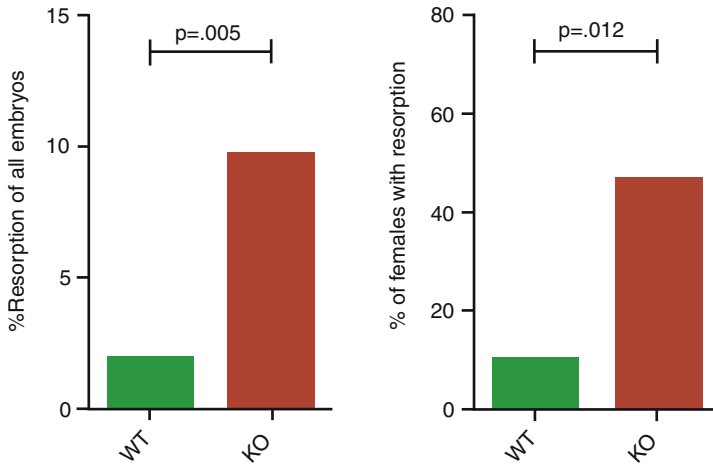


Fig. 4.2 Percent of resorbed embryos in CNS1-sufficient (wild type) and CNS1-deficient pregnancies in knockout mice

4.5 Dendritic Cells

Dendritic cells (DCs) are at the biological bridge between the innate and the adaptive immune system and their activation and modulation is critical for the outcome of the immune response. DCs localize in the peripheral tissue and act as sentinel of the immune response. After an inflammatory stimulus, DCs migrate via lymphatic vessels to the lymph node to present antigen to T cells [7]. According to their state (activated or not activated), DCs can secrete pro- or anti-inflammatory cytokines, thereby inducing immune responses or suppressing them, respectively.

In pregnancy, the number of DCs in the decidua is very low and the cells are phenotypically immature. The role of decidual DCs has not been fully elucidated; recently, it was suggested that DCs, as well NKs and macrophages, could act at the feto-maternal interface, intervening in the tissue remodeling and promoting maternal immune tolerance [7]. An increased number of phenotypically mature DCs have been associated with spontaneous miscarriage [24].

4.6 B Cells

B cells are a component of the humoral immunity of the acquired immune system. The main function of B cells is the production of antibodies (IgG, IgM, IgE, IgA), but B cells can also uptake, process, and present antigens and can produce several cytokines influencing immunity. The role of B cells during pregnancy has been poorly studied, but it was postulated that they may contribute toward pregnancy tolerance by regulating the production of the immune-modulatory cytokine IL-10 [25]. A physiological decrease of B cells was noted in the third trimester of normal

pregnancy while preeclampsia has been associated with a persistence of a higher number of B cells. In women with autoimmune disease, it is possible that B cells compromise gestation, producing excessive autoantibodies [25].

4.7 Trophoblast as Regulator of Innate Immune Cell

Trophoblastic cells express pattern recognition receptors that act as “sensors” of the surrounding microenvironment [5]. These sensors allow the recognition of the presence of bacteria, viruses, damaged tissues, and dying cells by the trophoblast. Trophoblastic cells can secrete a specific set of cytokines influencing the immune cells within the decidua with the aim of instructing inflammatory cells to create an adequate microenvironment, to promote pregnancy evolution [5]. The success of the pregnancy depends on the trophoblastic ability to communicate with any immune cell type (monocytes/macrophages, pTreg and NK cells) and to coordinate their interrelated work [5, 26].

4.8 The Alteration of the Maternal–Fetal Equilibrium of the Inflammatory Cells

Alterations in type, number, aspect, or interrelationship of any component of the cells of the inflammatory milieu may be detrimental for pregnancy outcome. This might be the consequence of infections or of maternal immunological problems, either in clinical or in subclinical conditions.

Infection can reach the placenta and the fetus through the maternal blood circulation or by ascending into the uterus from the vagina or by descending into the uterus from the peritoneal cavity, by activation of the pathogenic phenotype of preexisting bacteria, or even by sudden immune reaction toward preexisting symbiotic bacteria.

4.8.1 Acute Chorioamnionitis

These processes could develop into acute chorioamnionitis. In these cases, most of infecting agents originate in the cervicovaginal tract and gain access to the uterine cavity breaching the normal cervical barrier. Maternal neutrophils infiltrate the chorionic plate and membranous chorioamnion (Fig. 4.3) [27]. Normally, neutrophils are a population of inflammatory cells that do not infiltrate placental compartments. When an infective insult occurs, neutrophils can invade placental structures; they can derive both from the intervillous space and the venules of decidua capsularis. In case of acute chorioamnionitis, a maternal and/or a fetal inflammatory response should be distinguished. The stage (progression of the disease) and the grade (intensity of the disease) of the inflammatory response are summarized in Table 4.2. Acute chorioamnionitis has been associated with adverse pregnancy and neonatal outcome, in relation to prematurity due to preterm delivery and/or preterm premature rupture of the membrane [29]. Fetal inflammatory response is the main factor that affected fetal–neonatal well-being; fetal inflammatory response involves

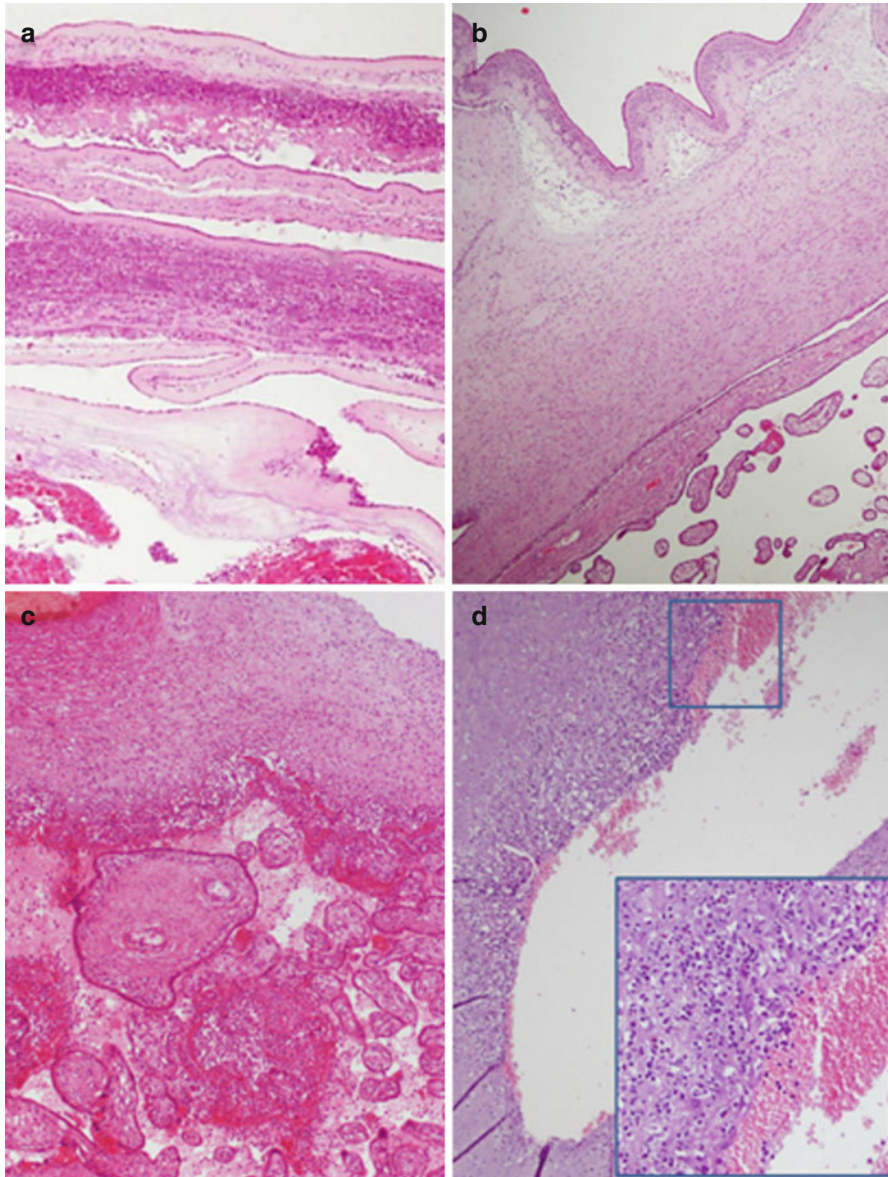


Fig. 4.3 Placental acute inflammatory lesions. Images show maternal and fetal inflammatory response in term placentas. *A* severe acute chorioamnionitis in the free membranes; note the patchy–diffuse accumulations of neutrophil in the subchorionic plate, involving also the chorion and amnion. *B* severe acute chorioamnionitis in the placental chorionic plate, involving both the amnion and chorion. *C* severe acute chorioamnionitis with acute intervillitis. Note the large accumulations of neutrophils (microabscesses) under the chorion and between placental villi. *D* fetal inflammatory response involving the umbilical vein. Note the accumulation of the inflammatory infiltration across the wall of the vessel

Table 4.2 Stages and grades of acute chorioamnionitis

Maternal inflammatory response		Fetal inflammatory response	
Definition	Description	Definition	Description
Stage 1 Acute subchorionitis/ acute chorionitis	Patchy–diffuse accumulations of neutrophil in the subchorionic plate fibrin and/or membranous chorionic trophoblast layer	Chorionic vasculitis/ umbilical phlebitis	Neutrophils in the wall of any chorionic vessel or in the umbilical vein
Stage 2 Acute chorioamnionitis	More than a few scattered neutrophils in the chorionic plate or membranous chorionic connective tissue and/or the amnion	Umbilical vasculitis	Neutrophils in one or two arteries and/or in umbilical vein
Stage 3 Necrotizing chorioamnionitis	Degenerating neutrophils (karyorrhexis), thickened eosinophilic amniotic basement membrane, and at least focal amniotic epithelial degeneration	Necrotizing funisitis or concentric umbilical perivasculitis	Neutrophils, cellular debris eosinophilic precipitate, and/or mineralization arranged in a concentric band around one or more umbilical vessels
Grade 1 Mild–moderate	Individual or small clusters of maternal neutrophils diffusely infiltrating amnion, chorionic plate, chorion leave, and/or subchorionic fibrin	Mild–moderate	Scattered neutrophilic infiltrate in the subendothelial or intramural portion of the vessel
Grade 2 Severe	Three or more chorionic microabscesses between the chorion and decidua in the membranes and/or under the chorionic plate or a continuous band of a confluent chorionic polymorphonuclear leukocyte	Severe	Vessels with near confluent neutrophils with attenuation and/or degradation of vascular smooth muscle cells

Modified from Redline et al. [28]

chorionic plate vessels and/or umbilical vein prior to the involving of umbilical arteries. The association between fetal inflammatory response and adverse neonatal condition and outcome takes place especially when umbilical arteries are involved. Neonatal sepsis could be a consequence of fetal inflammatory response but also neurological impairment may develop including cerebral palsy [30].

When fetal neutrophils are found in fetal capillaries and stroma of distal villi, with minimal intervillous component, the lesion is called *acute villitis* and it could represent an expression of intrauterine fetal sepsis due to a bacterial hematogenous infection such as *Escherichia coli* or group B streptococcus.

4.8.2 Chronic Chorioamnionitis

The differential diagnosis of acute chorioamnionitis includes chronic chorioamnionitis, a placental lesion characterized by an infiltration of maternally derived T lymphocytes CD3⁺ in the chorioamniotic membranes [27]. Viral infection can be associated with chronic chorioamnionitis, but the actual cause of this lesion is still unknown. A frequent association between chronic chorioamnionitis and villitis of unknown etiology and the altered chemokine profile observed in the amniotic fluid of cases affected by chronic chorioamnionitis permit to hypothesize an immunological cause of this histological placental lesion, suggesting a reaction consistent in maternal anti-fetal rejection [31, 32]. Chronic chorioamnionitis has been associated with spontaneous preterm birth and intrauterine fetal growth restriction [27].

4.8.3 Chronic Villitis of Unknown Etiology

Chronic villitis of unknown etiology is a placental lesion characterized by the presence of villous mononuclear cell infiltrates composed of maternal CD8⁺ T lymphocytes [33]. An increased number of placental Hofbauer cells may coexist and a histiocytic infiltrate within the intervillous space (chronic intervillitis) may accompany the chronic villitis. The origin of this lesion is still unknown but a maternal immune response against the fetus has been advocated, similar to host-versus-graft rejection [33]. Although a low grade of villitis of unknown etiology could affect placentas from normal pregnancies without clinical consequences, high-grade lesions could be associated with severe abnormal pregnancy outcome. Clinical associations are summarized in Table 4.3. Recurrent villitis in the subsequent pregnancies is associated with maternal obesity (a known condition of immune dysfunction) and multigravidity (in relation to the repeated exposure to the fetal antigens).

4.8.4 Chronic Villitis in Oocyte Donation

Pregnancies derived from donated oocyte also present a high prevalence of villitis of unknown etiology. Egg donation pregnancies represent an interesting challenge for the fetomaternal interface immunological aspect: the mother must tolerate a

Table 4.3 Chronic Villitis of unknown etiology

Grade	Histological features	Distribution	Association with other placental lesions	Possible clinical association
Low	Lesion affecting less than 10 villi per focus	Focal (only one slide involved) Multifocal (more than one slide involved)	No specific association	No specific association
High	More than 10 villi affected per focus	Patchy Diffuse (involving more than 5 % of all distal villi) Involving proximal stem villi Involving anchoring villi and the adjacent terminal villi (basal villitis)	Diffuse perivillous fibrin deposition Obliterative fetal vasculopathy Chronic deciduitis with plasma cells	IUGR, IUFD, PD NE, CP PL, SM

CP cerebral palsy, *NE* neonatal encephalopathy, *IUGR* intrauterine fetal growth restriction, *IUFD* intrauterine fetal death, *PD* preterm delivery, *PL* periventricular leukomalacia, *SM* spontaneous miscarriage

completely allogenic conceptus. The higher incidence of villitis of unknown etiology, as well as other placental histological lesions (chronic deciduitis, massive chronic intervillitis, increased infiltration of T-helper cells, and natural killer cells), in the basal plate of egg donation pregnancies seems to be related to a more pronounced immune-mediated response in this particular type of medical achieved pregnancies. The placental histological damages and the frequently abnormal clinical evolution of egg donor pregnancies may be the consequence of a reaction similar to graft-versus-host disease and/or organ rejection [34].

4.8.5 Chronic Deciduitis

Chronic deciduitis corresponds to a mixed lymphoplasmacytic infiltrate in the decidua, identifiable either in the free membrane or along the maternal surface, sometimes encroaching the anchoring villi. The presence of plasma cells in the endometrium is always considered an abnormal feature (Fig. 4.4). It may develop as a consequence of antigen-stimulating events related both to infection and noninfection insults [35]. A source of antigen is bacterial subacute endometritis that may cause recurrent acute chorioamnionitis and preterm delivery in the subsequent pregnancies [36]; otherwise, an alloimmune response may be at the base of chronic deciduitis. When there is not an acute inflammation, decidual plasma cells are associated with infertility, miscarriage, and chronic villitis [28].

In summary, an acute neutrophilic infiltrate of the placenta is generally related to infective insults, as occurs in acute chorioamnionitis; a chronic placental inflammatory infiltrate (including lymphocytes, histiocytes, plasma cells) generally represents

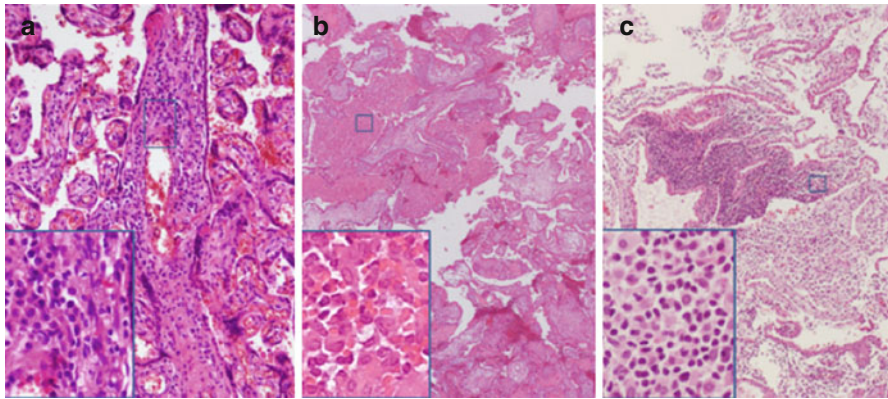


Fig. 4.4 Chronic placental inflammatory lesions. *A* chronic villitis of unknown etiology. Note the inflammatory infiltration within the placental villi. The *inset* permits to appreciate the characteristic predominant lymphocytic composition of the infiltrate. *B* chronic intervillitis. Note the aggregates of inflammatory cells in the intervillous space admixed with fibrin deposition. The *inset* permits to appreciate the characteristic predominant histiocytic composition of the infiltrate. *D* chronic deciduitis in first trimester spontaneous miscarriage. Note the massive plasma cells infiltration within the decidua (*inset*)

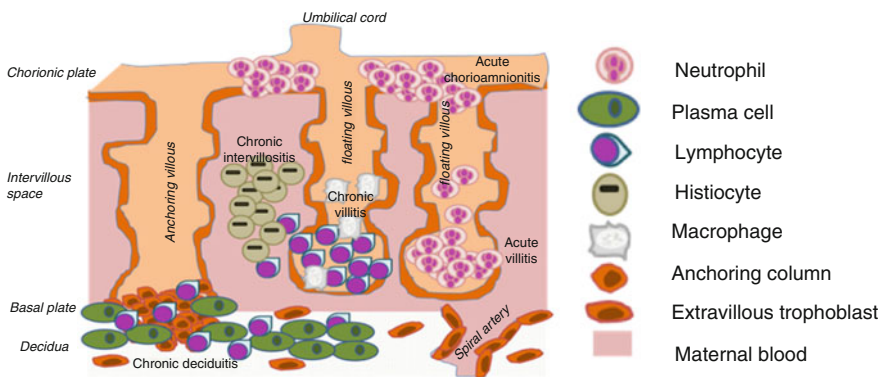


Fig. 4.5 Schematic example of the distribution of inflammatory cells during placental pathology. Many types of inflammatory cells may pathologically inhabit multiple compartments of the placenta, leading to damages of placental function and conducting to adverse pregnancy outcome. For a detailed description of any lesions, see the text

an inflammatory noninfective placental reaction, as occurs in chronic villitis, chronic chorioamnionitis, chronic intervillitis, and chronic deciduitis. These four last lesions often coexist as a tetrad, suggesting an alloimmune response. Maternal characteristics such as obesity and autoimmune disease (including systemic lupus erythematosus, antiphospholipid syndrome, type 1 diabetes mellitus, and thyroiditis) could constitute a predisposing factor for the development of these placental damaging lesions.

Schematic exemplification of the distribution of the inflammatory cell during the placental lesions is shown in Fig. 4.5

4.9 Inflammatory Lesions of the Decidua

Annetine Staff defines the decidua basalis “the decidual battleground” [37]. This is the place, the no man’s land, where all these cells rush, live, cooperate, and fight in human reproduction. A more subtle immune-inflammatory lesion that dramatically impacts on placental function in late gestation is acute atherosclerosis. This lesion affects 20–40 % of cases of late preeclampsia but is observed also as a minor lesion in a subset of “normal” pregnancies, suggesting a continuum of unbalanced interaction from subclinical to clinical to severe disease. This local process occurs without systemic vascular lesions. Histologically acute atherosclerosis is characterized by CD68-positive subendothelial lipid-filled foam cells. These cells derive macrophages and possibly smooth muscle cells. This process is associated with an infiltration of inflammatory mononuclear cell like early stages of atherosclerosis in coronary artery disease. This lesion is seldom seen in the myometrial tract of spiral arteries and is not caused by hypertension. This process is immune-inflammatory in nature and not caused by dyslipidemia. It might be observed in pregnancies with fetal growth restriction and immune diseases. It is of interest to observe that this lesion might be found not only in abnormal spiral arteries as per early shallow trophoblastic invasion but also and mainly in normal spiral arteries. Atherosclerosis ignites a vicious circle of under-perfusion, oxidative stress, inflammation, and atherosclerosis. According to Staff and coworkers [38], the hyperlipidemia of normal pregnancy worsens in women with a pro-atherogenic lipid profile that develop preeclampsia.

These recent findings suggest a possible link between low-grade inflammation, dyslipidemia that characterize metabolic syndrome and excess, and/or severity of late gestation acute atherosclerosis and late preeclampsia, associated with a normal fetal growth.

The full understanding of these pathological concepts should induce clinical counselors to underline the importance of prepregnancy lifestyle and nutrition for a successful pregnancy.

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