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Villitis of unknown etiology: noninfectious chronic villitis in the placenta

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Summary Villitis of unknown etiology (VUE) is an important pattern of placental injury occurring predominantly in term placentas. Although overlapping with infectious villitis, its clinical and histologic characteristics are distinct. It is a common lesion, affecting 5% to 15% of all placentas. When low-grade lesions affecting less than 10 villi per focus are excluded, VUE is an important cause of intrauterine growth restriction and recurrent reproductive loss. Involvement of large fetal vessels in the placenta (obliterative fetal vasculopathy) in cases of VUE is a strong risk factor for neonatal encephalopathy and cerebral palsy. Although the etiology of the eliciting antigen is unknown, many other characteristics of the immune response have been clarified. VUE is caused by maternal T lymphocytes, predominantly CD8-positive, that inappropriately gain access to the villous stroma. Fetal antigen-presenting cells (Hofbauer cells) expand and are induced to express class II major histocompatibility complex molecules. Maternal monocyte-macrophages in the perivillous space likely amplify the immune response. Although much speculation exists that VUE represents a host-versus-graft reaction analogous to transplant rejection, other eliciting antigens have not been excluded. Irrespective of target antigen or antigens, the pathophysiologic implications of having activated maternal lymphocytes within vascularized fetal tissues are not trivial.

1. Introduction

Chronic villitis is defined by the presence of a lymphohistiocytic infiltrate affecting varying proportions of the villous tree of the placenta. It is a relatively common process affecting between 5% and 15% of all third-trimester placentas, yet in a historical sense analogous to chronic *Helicobacter pylori*–associated gastritis, it was largely overlooked before Altshuler and Russell's [1] influential review published in 1975. The primary purpose of that review was to highlight the association of chronic villitis with congenital infections. In the course of exhaustively cataloguing the literature regarding the nature of the placental inflammatory response to these organisms, they were the first to call attention to the category of villitis of unknown etiology (VUE). They documented its frequency (>5% of all term births), the 3 common histologic patterns (focal, diffuse, and basal), its association with intrauterine growth restriction, and emphasized the lack of evidence for an underlying microbial etiology.

The most common currently recognized infectious causes of chronic villitis in the United States are *Treponema pallidum*, cytomegalovirus, and to a lesser extent *Toxoplasma gondii*. A fourth major cause, rubella virus, has virtually been eliminated by the rubella vaccination program

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introduced on a wide scale after the rubella pandemic of 1964. Table 1 lists some of the distinguishing characteristics separating infectious villitis from VUE. Among the most important are the absence of signs and symptoms of infection in either mothers or infants with VUE, the wide disparity in relative frequency (approximately 1-4/1000 livebirths versus 50-150/1000 for VUE), differing times of onset (late second–early third trimester for infectious villitis versus late third trimester for VUE), more diffuse involvement of villi and other placental regions in infectious villitis, increased proportion of lymphocytes in VUE, and the presence of specific histologic characteristics such as villous plasma cells, hemosiderin deposits, and umbilical cord organisms in infectious villitis.

One hypothesis to explain some of these differences is that VUE is the result of infection of the placenta by common bacteria or viruses that do not spread to the fetus. Rare cases of chronic villitis after maternal enteroviral infections support such a hypothesis [2]. However, the absence of any preceding maternal illness, the lack of seasonal variation, and the negativity of viral cultures and serology when available, plus certain characteristics of VUE to be discussed later such as recurrence, increased prevalence in multigravidas, and association with ovum donation pregnancies argue against this hypothesis for most cases. Some recent studies have suggested that clinically silent placental coxsackievirus infections may be a frequent cause of unexplained adverse pregnancy outcome [3,4]. However, these as yet unconfirmed studies did not detect a concomitant inflammatory response to viral antigen and hence are not relevant to VUE. One study using electron microscopy detected virus-like particles in 41% of VUE cases. However, the lack of commonality in these "particles" and the failure to find any evidence of infection in the remaining 59% of cases argue against a viral etiology for most cases [5]. Although unusual examples of bacterial villitis mimicking VUE have been reported [6], a recent study using polymerase chain reaction for 16S ribsosomal sequences shared by all eubacteria found no evidence of a bacterial etiology in 19 consecutively studied cases [7].

Table 1 Distinction between infectious villitis and VUE

	Infectious villitis	VUE
Incidence	1-4/1000	76-136/1000
Stage of pregnancy	Premature	Term/near term
Recurrence	Rare	10%-15%
Severity in recurrence	Less	Greater
Maternal illness	Yes	None
Fetal infection	Yes	None
Extent of involvement	Umbilical cord, chorionic plate, membranes—common	Terminal and stem villi only
Pattern of involvement	All villi abnormal, varying severity	Focal/patchy, others normal
Duration of involvement	Long-standing with fibrosis and calcification	Recent with fibrin and necrosis
Histology	Diffuse histiocytic villitis fibrosclerosing villitis plasma cell villitis	Lymphohistiocytic villitis

The entity known as VUE remains poorly understood and controversial in 2007. It is one of the commonest lesions seen in third-trimester placentas, yet it is still commonly under recognized (and, paroxically, sometimes overdiagnosed) by pathologists. Many physicians and investigators outside of pathology have never heard of the lesion and have no appreciation of its biologic and clinical significance. Among perinatal pathologists, there remain passionate advocates favoring either an underlying infectious etiology or the hypothesis that VUE represents an allogeneic transplantation rejection reaction. This controversy will not be settled here, nor will it ever truly be settled because the possibility of a previously unrecognized pathogen can never be excluded. The purpose of this review is to provide for pathologists, clinicians, and reproductive biologists a current review of the histopathologic spectrum, clinical associations, underlying pathogenesis, and adverse outcomes accompanying this important pattern of placental injury.

2. Pathology

VUE is a common lesion. Two large series of 1000 and 7505 consecutively examined placentas reported overall prevalences of 13.6% and 7.6% [8,9]. When cases with only 1 to 2 small foci were excluded from the former study, the prevalence was 8.7%, which agrees quite closely with my own experience with 3 large cohorts studied over a 20-year period in 2 separate geographical locales in the United States. I personally do not make a diagnosis of chronic villitis based on a single focus of VUE involving less than 5 villi. Although the incidence increases depending on the number of sections examined, the detection rate peaks at 4 sections, and about 90% of cases are detected with a standard sampling of 2 to 3 blocks [8]. VUE is primarily seen in term placentas with more than 80% of cases presenting at greater than 37 weeks and virtually all of the remainder after 32 weeks [10]. A finding of chronic villitis at less than 32 weeks should increase the suspicion for an infectious etiology.

One of the cardinal characteristics distinguishing VUE from infectious villitis is nonuniform involvement of the placental parenchyma. With the exception of some reactive hypervascularity in surrounding villi, unaffected portions of the placenta are usually completely normal. Although past classifications have separated VUE into focal and diffuse subgroups, in reality it is unusual for even the most severely affected placenta to show more than 10% total involvement. My personal preference is to distinguish cases based on the number of villi involved per focus. When less than 10 villi are involved, the

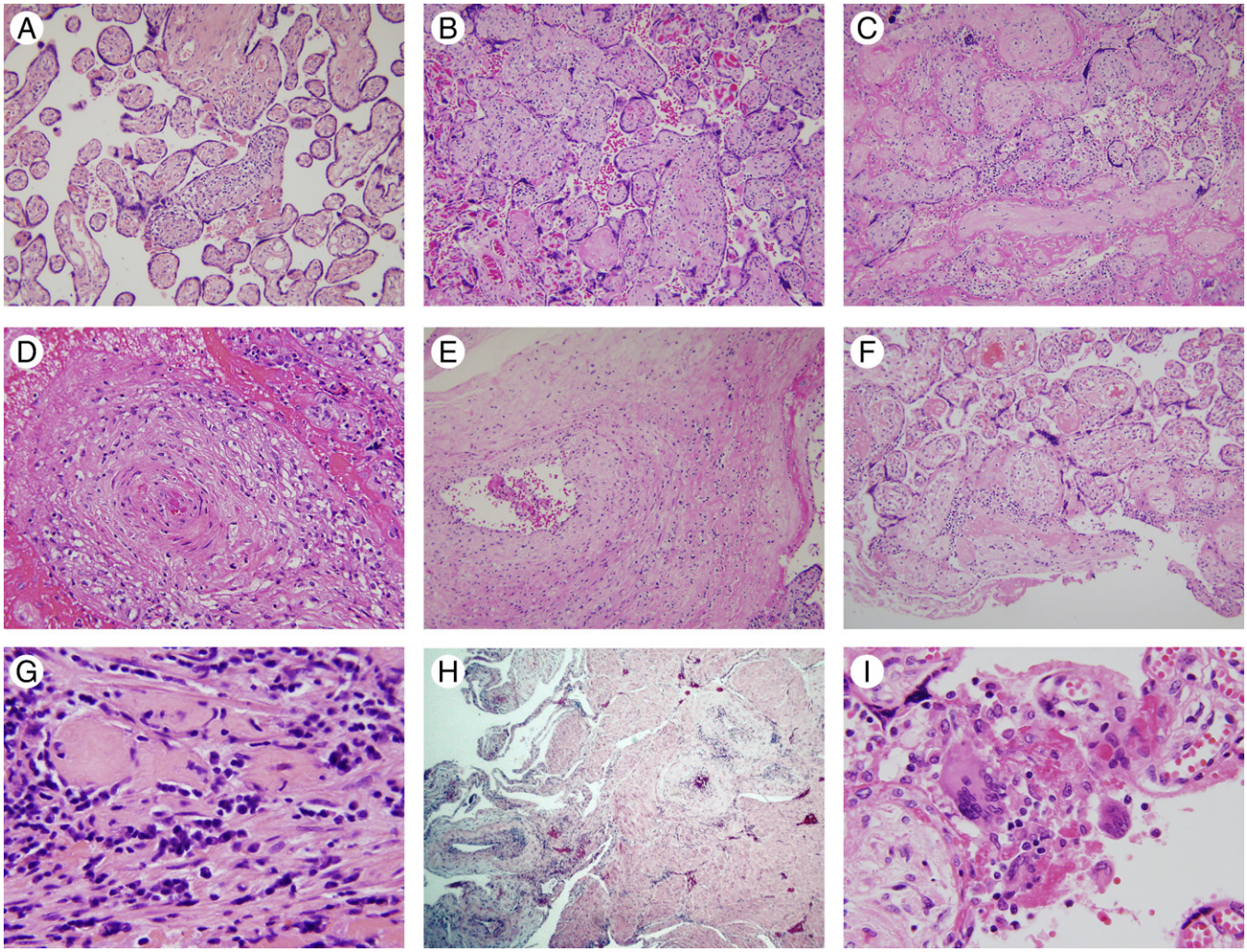

Fig. 1 Histologic characteristics of VUE. A, Low-grade chronic villitis (<10 inflamed villi per focus). Two terminal villi plus an adjacent portion of a mature intermediate villus show an irregularly distributed, lymphocyte-predominant inflammatory infiltrate sharply circumscribed from adjacent normal villi (original magnification ×100). B, High-grade chronic villitis (>10 inflamed villi per focus). Numerous contiguous distal villi show an irregular lymphohistiocytic infiltrate with mild fibrosis and vascular involution of the villous stroma. A few contiguous normal villi are seen at the top of the field (original magnification ×100). C, Diffuse chronic villitis with extensive perivillous fibrin. Numerous chronically inflamed villi in varying stages of degeneration are embedded in a meshwork of adherent perivillous fibrin and inflammatory cells (original magnification ×100). D, Proximal villitis—stem villitis and obliterative fetal vasculopathy with vascular occlusion. This large stem villous shows a large vessel with fibro-obliterative changes and focal thrombosis surrounded by a chronic perivasculitis (original magnification ×400). E, Proximal villitis—chronic chorionitis and chorionic vasculitis. Maternal lymphohistiocytic cells are observed in the subchorionic fibrin, chorionic stroma, and lower vascular wall. Both the muscularis and intimal regions are involved. Of note, inflammatory cells are not observed in the amniotic fluid-facing wall (upper left) or the endothelial lining of the chorionic vessel (original magnification ×100). F, Basal villitis. There is a mild lymphocytic infiltrate surrounding and focally infiltrating villi embedded in and adjacent to the decidua basalis that shows a chronic deciduitis (original magnification ×100). G, Lymphoplasmacytic deciduitis. Maternal decidua basalis is suffused with mixed infiltrate of small lymphocytes and plasma cells (original magnification ×400). H, Gravid hysterectomy from pregnancy with diffuse chronic villitis of the placenta. Chronic inflammatory cells surround and focally infiltrate the wall of large myometrial arteries (original magnification ×20). I, Focal perivillitis with histiocytic giant cells. Small lymphocytes, monocyte-macrophages, and a few histiocytic giant cells are enmeshed in loose perivillous fibrin adjacent to a focus of chronic villitis (original magnification ×400).

process is *low grade* and can be termed either *focal* (only one slide involved) or *multifocal* (more than one slide involved) (Fig. 1A). *High-grade chronic villitis*, on the other hand, has more than 10 villi per focus (Fig. 1B). It is separated into *patchy* and *diffuse* subgroups with the latter term being used when more than 5% of all distal villi are involved. One study has validated this approach showing that the risk of adverse neurologic outcome is increased only in those infants whose placentas show high-grade villitis [11]. *Diffuse chronic villitis* is commonly associated with diffuse perivillous fibrin deposition, a process that can markedly increase the risks of intrauterine growth restriction (IUGR), premature delivery, and stillbirth (Fig. 1C). Cases of diffuse villitis with

extensive perivillous fibrin deposition are also more likely to recur in subsequent pregnancies in my experience.

VUE shows several distinct patterns of involvement. Approximately half of all cases are exclusively localized to *distal villi* (terminal and mature intermediate villi) with sparing of the chorionic plate, proximal stem villi, and anchoring villi embedded in the basal plate. The second most common pattern (approximately 30% of cases) is chronic villitis involving *proximal stem villi* (and sometimes chorionic plate), usually together with distal villi. This pattern is often associated with fetal vascular obstructive lesions termed *obliterative fetal vasculopathy* [12]. Obliterative fetal vasculopathy is characterized by perivasculitis and varying degrees of true vasculitis involving stem villous and/or chorionic vessels (Fig. 1D and E). Inflammation in this process leads to luminal obliteration and/or thrombosis resulting in large regions of downstream avascular villi. *Extensive avascular villi* are also observed in fetal thrombotic vasculopathy (FTV) [13]. Because FTV is generally associated with chronic umbilical cord occlusion and, unlike VUE, has a low recurrence rate, these processes should be distinguished if possible. This is not always straightforward [14]. For example, focal VUE in a case with extensive fetal vascular thrombosis and avascular villi may reflect localized breakdown of the trophoblastic barrier secondary to ischemia, allowing maternal cells to enter the villous stroma (see below). However, in general, the presence of a significant component of villitis, particularly if present in proximal villi, should take the case out of the FTV category. The least common variant of VUE (approximately 20% of cases) is *basal villitis*, which predominantly involves anchoring villi embedded in the basal plate and adjacent terminal villi (Fig. 1F). *Basal villitis* is almost invariably associated with chronic deciduitis, usually with numerous plasma cells (*lymphoplasmacytic deciduitis*) (Fig. 1G). However, it should be noted that decidual plasma cells are also common in other forms of VUE being seen in approximately one third of all cases [15]. An interesting but anecdotal observation in a gravid hysterectomy specimen from a patient with VUE suggests that, in some cases, maternal inflammation extends deeper, surrounding arteries in the myometrium (Fig. 1H). All forms of chronic villitis may have a significant component of perivillous inflammation. Sometimes the intensity of the perivillous component exceeds that of the villitis. However, chronic perivillous inflammation in the absence of villous inflammatory cells excludes a case from the VUE category and other entities such as infections including malaria and idiopathic *chronic histiocytic intervillositis* should be considered [16,17].

The cellular composition of the inflammatory infiltrate in VUE is predominantly lymphocytes and macrophages, although the relative percentages of each vary from case to case. It is not uncommon to identify occasional histiocytic giant cells, especially in the perivillous component of the infiltrate (Fig. 1I). Although giant cells are also occasionally seen in some forms of infectious villitis (*Toxoplasma gondii* and *Trypanosoma cruzi*), their presence in a case of otherwise typical VUE should not raise the suspicion of an infectious etiology. Other more common causes of granulomatous inflammation such as mycobacterial and fungal infections do not cause chronic villitis. Lymphocytes in VUE are almost exclusively T cells with CD8 positivity predominating over CD4 in most cases (CD4/CD8 ratio range, 0.1-0.5) [18-20]. Macrophages are CD68- and HAM 56–positive, but generally Mac387-negative. Class II major histocompatibility complex (MHC) antigens are up-regulated on macrophages at sites of villitis [21]. The presence of activated macrophages and giant cells and the absence of eosinophils and mast cells suggest that VUE represents a delayed hypersensitivity type or T-helper-1-type response, although formal documentation by assessing the cytokine profile (interferon γ, interleukin [IL] 2, and tumor necrosis factor as opposed to IL-4, IL-5, or transforming growth factor β) is lacking. Neutrophils may be present in small numbers in cases with a prominent perivillous inflammatory component. If present in large numbers or if localized to the villous parenchyma, they should prompt a search for an infectious etiology [6]. Some observers have reported B cells and natural killer cells in VUE [19,22]. However, most studies have not found appreciable numbers of these cells. An exception is basal VUE where as many as 30% of cells are B lymphocytes [19]. Villous plasma cells are essentially never seen in VUE and, when identified, are strongly suggestive of cytomegalovirus or other viral infections [23].

3. Clinical associations

There are no specific clinical signs and symptoms suggesting a diagnosis of VUE. However, several studies have shown VUE to be associated with intrauterine growth restriction (IUGR) [8,9,24,25]. The frequency of IUGR with VUE is directly proportional to the extent of villous involvement. In one study, VUE was the most frequent pathologic finding in normotensive-term pregnancies with antenatally diagnosed IUGR [24]. This study also reported associations of VUE with oligohydramnios and chronic monitoring abnormalities including abnormal nonstress testing, abnormal pulsed flow Doppler studies, and abnormal biophysical profile. Although ethnic origin has not been evaluated in the United States, a large study from New Zealand found VUE to be more common in whites than either in Maoris or mothers of Asian ancestry [25]. This study also found that VUE was significantly more common in obese women. Although far from settled, large placentas from obese women often have an increase in villous macrophages (Hofbauer cells) that could increase the efficiency of antigen presentation leading to VUE (see below). VUE is more frequent and, in some unpublished data from one of our previous studies, more likely to be diffuse in multigravid mothers [24,25]. Both suggest that prior antigen exposure might play some role in its

pathogenesis. A role for prior sensitization is further supported by the elevated risk of recurrent VUE in women with previous affected pregnancies [26]. VUE has a higher than expected concordance in twin placentas [27]. This risk was elevated for separate diamnionic dichorionic placentas (43%), increased still further for fused diamnionic dichorionic placentas (56%), and reached 100% for a monochorionic placenta. These results suggest that systemic factors such as maternal sensitization make simultaneous occurrence in separate twin placentas more likely, but that local factors also play a role since fused and monochorionic placentas showed a higher concordance than separate ones. Two studies have demonstrated an increased incidence of VUE in placentas derived from ovum donation pregnancies compared with placentas from in vitro fertilization pregnancies where maternal ova were used [28,29]. These results suggest that either more foreign antigens or the absence of shared self-antigens in the placenta play a role in susceptibility [30]. Finally, a poorly understood correlation between neonatal alloimmune thrombocytopenia with VUE has been reported, particularly in untreated mothers (36% overall, 83% in the absence of therapy) [31]. Maternal antiplatelet antibodies in this condition could bind platelets or cross-reacting antigens on or within villi leading to antibody-dependent cellular cytotoxicity or immune complex–mediated injury. Alternatively, they may activate platelets allowing them to adhere to trophoblast and produce proinflammatory mediators that promote villous inflammation [32].

4. Pathogenesis

4.1. Origin of cells

As discussed above, VUE is a CD8-predominant, T-cell–mediated immune response developing in the fetal fibrovascular stroma of placental villi in the latter part of human pregnancy. One of the first questions was whether the inflammatory cells in VUE were derived from mother or fetus. Complementary techniques of determining sex chromosome composition in male placentas by in situ hybridization and immunocytochemical staining for specific maternal class II MHC antigens were used to address this question [33,34]. Both studies established that lymphocytes in VUE were of maternal origin. Hence, VUE was shown to be a host-derived inflammatory response occurring within a donor allograft tissue. Myerson and coworkers [35] recently clarified the origin of the non–T-cell component of the infiltrate demonstrating that most antigen-presenting cells were fetal macrophages (Hofbauer cells) but that histiocytic giant cells and some perivillous monocyte-macrophages were of maternal origin. Several investigators have shown that fetal Hofbauer cells proliferate in VUE and become activated as evidenced by up-regulation of class II MHC antigen expression [21,22,36].

4.2. Access to fetal tissues

It was once believed that the trophoblast surrounding placental villi formed a restrictive barrier blocking access of maternal cells to fetal antigens [37]. In this formulation, the lack of MHC antigen expression on syncytiotrophoblast "solved" the problem of why the placenta was not rejected by the mother. The high frequency of VUE is just one of several lines of evidence showing that maternal cells can and do gain access to fetal tissues. One observation attesting to the frequency of intimate contact between maternal CD4-positive T cells and fetal DC-SIGN–positive villous macrophages is the high transmission rate of HIV that has been shown to occur between these 2 cells [38]. Interestingly, this transfer is genetically restricted occurring far more commonly in fetal macrophages expressing high levels of the chemokine receptor CCR5 [39,40]. Recent studies have shown that maternal cells not only enter the placental villi but also the fetus itself [41]. Maternal microchimerism can, in some cases, result in an alloimmune component to what had previously been considered autoimmune diseases such juvenile myositis [42]. It is an open question whether maternal cellular infiltration of fetal tissues contributes to perinatal morbidity and mortality in some cases of VUE.

Maternal inflammatory cells could "cross-over" into fetal villous stroma in several ways. First, the villous trophoblastic barrier may be damaged. Syncytial knots are regularly shed from third-trimester villi, and in some cases, this process can denude the villous stroma [43]. Ischemic damage from maternal infarction or upstream fetal thrombosis could break down the barrier. Local activation of platelets, coagulation components, or complement by antiphospholipid or other antibodies might lead to necrosis of syncytiotrophoblast. Second, although syncytiotrophoblast does not usually express adhesion molecules, it can be induced to express intercellular adhesion molecule 1 in cases of VUE [44]. Other evidence suggests that E-selectin can be induced on villous trophoblast by lipopolysaccharide [45]. Finally, maternal lymphocytes may bypass the villous trophoblastic barrier entirely entering the fetal stroma via the anchoring villi, which lose their continuous layer of epithelial syncytiotrophoblast as they differentiate to become invasive intermediate trophoblast during the course of placental development. Decidual stromal cells express IL-15, a trophic factor for CD8-positive memory T cells [46,47]. Maternal lymphocytes trafficking through or responding to antigen in the decidua (chronic deciduitis) might become activated and find a facilitated pathway of entry at this location.

4.3. Target antigens

Maternal T lymphocytes encounter a variety of foreign antigens in fetal villous stroma. In addition to allogeneic class I and II MHC antigens, CD4- and CD8-positive T cells can respond to minor histocompatibility antigens such as

male H-Y antigens. Unique oncofetal antigens only exposed during development may also be perceived as foreign by maternal T cells not previously exposed to them during thymic ontogeny. All of these antigens can potentially be presented by fetal macrophages or endothelial cells (direct pathway) or by infiltrating maternal monocyte-macrophages (indirect pathway) in the perivillous region or the decidua. It has been shown that local indirect antigen presentation can augment the direct response in models of allograft rejection [48]. Finally, it should be emphasized that microbial antigens may also be presented to maternal T cells. Although one would expect both a fetal and maternal response to such exogenous antigens, the immaturity of the fetal immune system may result in predominance of the latter [37,49-52]. In fact, several studies have shown that maternal CD8-positive T lymphocytes are prominently represented in the inflammatory infiltrate associated with placental syphilis, toxoplasmosis, and trypanosomiasis [18,20].

4.4. Progression of inflammation

One outstanding question is, given the ubiquity of maternal cell traffic into fetal tissues, why VUE and particularly severe VUE with perinatal morbidity and mortality occur in only a subset of women. Two factors could potentially account for such variability. First, T cells in more severe cases may have undergone priming before the affected pregnancy, either by fetal MHC antigens during a previous pregnancy or by autoantigens or foreign antigens that cross-react with fetal alloantigen. Memory T cells require minimal additional stimulation to divide, produce cytokines, and acquire cytotoxic activity upon repeat antigen exposure [48]. As previously discussed, prior sensitization is supported by the findings that VUE is more frequent and severe in multigravidas and is often recurrent. Second, although primary immune responses in the index pregnancy would generally be less severe, the high precursor frequency of alloreactive T cells in some hosts and the capacity of antigen-presenting cells to respond to co-stimulatory signals could lead to clinically significant immune responses even in previously unprimed hosts [53]. Whether these primary responses would be initiated in the placenta or the draining maternal lymph nodes is controversial, but the resulting effector cells could certainly enter the placenta [54]. Costimulatory signals include CD40L, B7-1 and B7-2, IL-12, and complement activation products [55,56]. Several of these molecules such as IL-12 p35, B7, and C3 are underexpressed in fetal macrophages but can be up-regulated [49-51]. Potential triggers for up-regulation might include transient maternal infections, elevated microparticles in the maternal circulation, cytokines secreted by chronic inflammatory cells in the decidua, and "danger" signals such as nucleotides, hyaluronate, and heat shock proteins released at foci of placental necrosis [57-59]. Alternatively, progression could simply be a stochastic process that can occur in any case of VUE depending on the balance between feed-forward mechanisms such as increased production of chemokines and cytokines; up-regulation of class II MHC and chemokine/cytokine receptors; and induction of adhesion molecules such as intercellular adhesion molecule-1 and E-selectin and feedback inhibitory mechanisms such as T regulatory cells. Recent reports have demonstrated a dramatic increase in circulating T regulatory cells during pregnancy [60]. These cells, which can also be primed by previous antigen exposure, could enter fetal tissue, react to foreign antigens, and inhibit immune responses by a variety of mechanisms including expression of CTLA-4, which blocks co-stimulation and the secretion of immunosuppressive cytokines such as transforming growth factor β and IL-10 [61]. Interestingly, specific polymorphisms in the IL-10 gene promoter that regulate level of secretion have been shown to lower the risk of GVHD in human bone marrow transplants [62].

A second question is why VUE sometimes progresses to obliterative fetal vasculopathy. Inflammation could either spread within the villous stroma from distal villi to larger proximal villi or it could develop independently at each site. The patchy nature of VUE, the occasional finding of proximal villitis without distal involvement, and cases where chronic inflammatory cells can be seen migrating into the subchorionic fibrin from the intervillous space all argue for multifocal involvement. Although it is tempting to compare obliterative fetal vasculopathy to the arteriopathy seen in chronic transplant rejection, it arises in a different time frame—weeks rather than years. Most human vasculitides including those associated with accelerated transplant rejection are caused by either antibodies directed against components of the vessel wall or deposition of immune complexes [48,63]. The possible role of antibodies has not been investigated in this relatively recently described lesion. The degree of fibro-obliterative change seems out of proportion to the degree of inflammation in obliterative fetal vasculopathy, and vascular occlusion may reflect an intrinsic property of fetal placental vessels to constrict and undergo obliterative remodeling. Delivery, upstream vascular occlusion, and severe underperfusion of the intervillous space all trigger this response, which protects the infant from exsanguination and helps to match maternal and fetal perfusion. Vascular obliteration in response to chronic inflammation in VUE could protect the fetus by preventing alloreactive maternal lymphocytes from entering the fetal circulation.

5. Pregnancy outcomes

As with all potentially serious placental disease processes, the most common outcome of pregnancies complicated by VUE is a normal healthy baby. The most common clinical condition associated with VUE is IUGR, and growth-restricted infants have an increased risk of later adult diseases including obesity, diabetes, hypertension, and

coronary artery disease [64]. Although a recent study showed that women with VUE in more than one pregnancy did not have an overall increase in perinatal complications [65], a subgroup of these patients clearly develop worsening disease in each pregnancy and have recurrent pregnancy losses including stillbirths [26,66]. Women with multiple recurrences of VUE have been anecdotally reported to respond to immunomodulatory agents such as progesterone, corticosteroids, low-dose heparin, and intravenous immunoglobulin (IVIG), but the efficacy of these regimens has not been established by controlled studies [26]. It is tempting to postulate that these mothers are presensitized and able to mount secondary responses to paternal or oncofetal antigens, although there is at present no direct evidence to support or refute this hypothesis.

The second group of adverse outcomes related to VUE are short- and long-term neurologic abnormalities. An increased susceptibility to seizures was reported by Scher and colleagues [67]. We reported that high-grade VUE was significantly increased in infants with a variety of long-term neurologic deficits [11]. A subsequent larger study showed that VUE with obliterative fetal vasculopathy was one of several severe fetal thrombo-inflammatory lesions significantly associated with both neonatal encephalopathy and cerebral palsy in the absence of neonatal encephalopathy [68]. Affected infants in this study were also noted to have an increased prevalence of abnormal hematologic findings including elevated nucleated red blood cells (NRBC) and low platelets. It was hypothesized that severe fetal vascular lesions increase the risk of central nervous system injury by several mechanisms including placental dysfunction, predisposition to coagulation, and release of inflammatory cytokines, and possibly alloreactive lymphocytes, into the fetal circulation.

6. Conclusions

As reviewed above, VUE represents a maternal immune response to antigen in the fetal villous stroma. The nature of the antigen is the "unknown" aspect of this process. Much circumstantial evidence implicates a host-versus-graft reaction. If a placental infection is causative, it is unlikely to be one that crosses into the fetus. Regardless of the eliciting antigen, the clinical significance of VUE is clear. Although common as a focal or low-grade process, high-grade extensive VUE, especially when combined with obliterative fetal vasculopathy, is an important cause of IUGR, recurrent reproductive loss, and long-term neurodisability. Its diagnosis by pathologists and recognition by clinicians are important for patient care. Awareness of this fascinating process should stimulate further investigation into some of the unanswered questions regarding its pathogenesis and implications for the maternal fetal immunologic relationship.

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