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The fetus, not the mother, elicits maternal immunologic rejection: lessons from discordant dizygotic twin placentas

Kamran Yusuf[1] and Harvey J. Kliman[2,*]

[1] Department of Pediatrics, University of Calgary, Alberta, Canada
[2] Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT, USA

Abstract

Aims: Our objective was to elucidate the pathogenesis of twin discordance in four dizygotic pregnancies where only one of the twins had IUGR due to chronic villitis.
Methods: We identified four cases of dizygotic twin placentas over a period of four years with evidence of chronic villitis. There was no clinical or pathologic evidence of TORCH, bacterial infection, preeclampsia or autoimmune disorders. Placentas were weighed, processed for histologic examination and stained with CD-45RO (clone UCHL1) mouse monoclonal antibody, which identifies T-cells.
Results: All placentas were dichorionic, with two being fused. Birth weight differences were 29%, 41%, 17% and 10%. Villitis was more marked in the placenta of the twin that weighed less and correlated with the degree of weight discordance. On examining the junction between the fused dichorionic placentas, the chorionic villi from the smaller twin contained numerous T-cells, whereas the villi associated with the less affected twin, showed little to no T-cells.
Conclusion: We describe a series of dizygotic twin placentas where the more severe the chronic villitis, the more affected the placenta and fetus. Since the maternal environment was constant for each of these twins, differences in villitis severity appears to be attributable to differences in the ability of each placenta to induce a maternal immune response.

Keywords: Dizygotic; fetus; IUGR; maternal immunologic rejection; placenta; twin; villitis.

*Corresponding author:
Harvey J. Kliman, MD, PhD
Yale University School of Medicine
Reproductive and Placental Research Unit
Department of Obstetrics, Gynecology and Reproductive Sciences
333 Cedar Street, 339 FMB
New Haven, CT 06520-8063
USA
Fax: +1 203 785-3854; +1 203 785-4477
E-mail: harvey.kliman@yale.edu

Introduction

Chronic villitis is a placental lesion associated with idiopathic intrauterine growth restriction (IUGR) and is characterized by the presence of mononuclear inflammatory cells in the fetal stroma of placental villi. The cellular infiltrate can be either focal or diffuse [18]. The reported incidence of chronic villitis in placentas has varied from 6% in the US to 33.8% in Argentina [7]. Although chronic villitis has been described in normal placentas, it is associated with significant perinatal mortality and morbidity [21]. Chronic villitis is associated with both IUGR and recurrent pregnancy loss with the severity of the villitis generally corresponding with the severity of clinical outcome [18, 33, 36]. Chronic villitis has been described in preeclampsia and maternal autoimmune disease [7, 18, 33]. Infections are also a known cause of chronic villitis, with the TORCH group of infections being implicated most commonly [6, 7, 12, 33]. However, there are cases of chronic villitis where no specific etiology can be determined, and this condition has been labeled as villitis of unknown etiology (VUE) [11, 34]. The source of the inflammatory cells in VUE, whether fetal or maternal, has been the subject of much controversy [34]. It has been suggested that such cases of chronic villitis may have an immunological basis and represent host versus graft disease with the mother mounting an immunological attack against paternally derived fetal antigens [17, 20, 36]. Using an *in situ* hybridization technique for X and Y-chromosomes, Redline and Patterson et al. [37] have demonstrated that the majority of lymphocytes in chronic villitis are of maternal origin, lending support to the hypothesis. Labarrere and Faulk et al. [23] using a double antibody technique in placentas that were mismatched for maternal-fetal HLA-DRw52 antigen have also demonstrated that the inflammatory cells in chronic villitis are derived from the mother. More recently, Myerson et al. [28], using conjoint immunohistochemistry-*in situ* hybridization (IHC-ISH), which allowed simultaneous visualization of both the karyotype and immunological phenotype of individual cells in paraffin embedded sections under light microscopy, demonstrated that lymphocytes in VUE are of maternal origin.

We describe here a series of four dizygotic twin pregnancies with dichorionic placentas wherein one of the placentas in each of these four twin pregnancies had evidence of a more severe chronic villitis. Analysis of these four dizygotic twin placentas allowed us a unique opportunity to elucidate the pathogenesis of the discordance

in villitis between the two placentas and discordance in birthweights of the twins. We believe this was due to an immunological response of the mother against the placenta of the affected fetus.

Materials and methods

The study was conducted at the Yale University School of Medicine and Yale New Haven Hospital and was approved by the Human Investigation Committee at Yale University. During the period of the study, there were approximately 5000 deliveries annually and approximately 15–20% of placentas were submitted for pathological examination by obstetricians. We identified four cases of dizygotic twin placentas, which had evidence of chronic villitis. These were all from spontaneous twin pregnancies. Charts from both the mother and babies were reviewed. In all cases serological tests for rubella and syphilis were negative in the mother and baby. None of the babies had any clinical evidence of a TORCH infection. Placental sections did not show any evidence of viral infection, toxoplasma cysts, or any other histopathological features of TORCH infections, such as the presence of calcifications, plasma cells or nuclear inclusions. There was also no evidence of a bacterial intrauterine infection in any of the cases examined. None of the mothers had preeclampsia.

Placentas were weighed after removing the umbilical cord, membranes and as much blood as possible. The placental weight was plotted on a centile chart as described by Pinar et al. [31]. Full thickness blocks from three sites in the placenta equidistant from the center and corresponding to the three angles of an equilateral triangle were obtained. One section was also taken from each cord and the membranes. These blocks were fixed in 10% formalin and stained with hematoxylin and eosin. In addition, sections were stained with CD45RO (clone UCHL1, M0742) mouse monoclonal antibody (DAKO, Carpinteria, CA), which identifies T-cells, myelomonocytes, but not B or NK cells. Severity of villitis was graded according to the method described by Knox and Fox [18] , as illustrated in Figure 1.

Placentas were labeled as A or B according to birth order, with A representing the first twin and placenta and B, the second twin and placenta. The degree of discordance was determined by dividing the weight difference between the heavier and lighter twin by the weight of the heavier twin and multiplying by 100. Birth weight discordance was defined as $>20\%$.

Results

Details of the four twin pregnancies are given in Table 1. The mean maternal age was 37.3 ± 6.6 years with the median being 32 years. The gestational age ranged from 33 to 37 weeks. Two of the mothers (case #s 2 and 3) had a previous history of pregnancy loss. All the placentas were dichorionic with two being fused. There were birth weight differences of 29%, 41%, 17% and 10% in the cases examined. Villitis was always more marked in the placenta of the twin that weighed less. The degree of weight discordance also correlated with the degree of villitis (Figure 2). The placentas with the severest degree of villitis were associated with a stillbirth at 37 weeks, an early neonatal death with pulmonary complications and a twin with thrombocytopenia and disseminated intra-

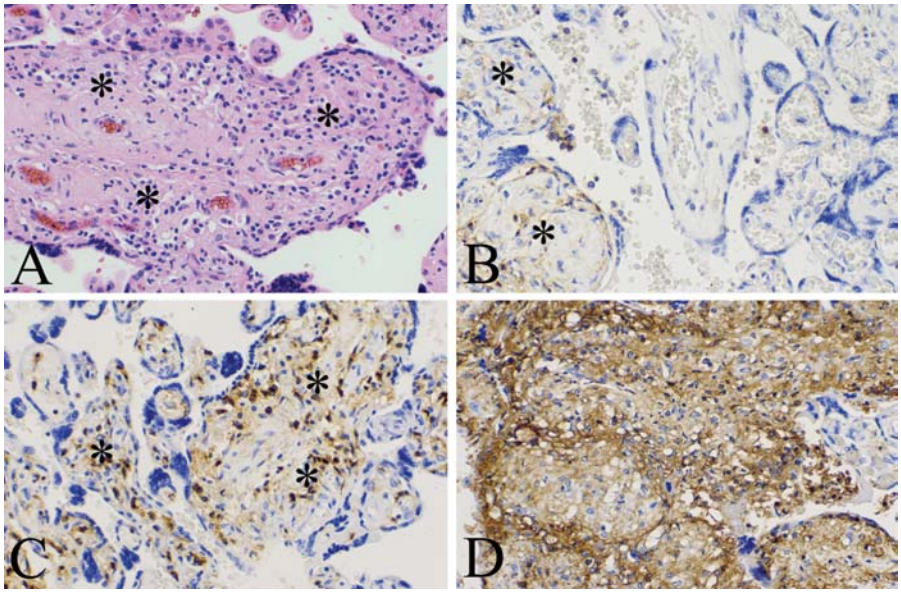

Figure 1 Grading of chronic villitis. (A) Hematoxylin and eosin stained chorionic villus with many lymphocytes within the villus core (*) consistent with moderate chronic villitis. (B) CD45RO stained chorionic villi with occasional lymphocytes noted within a few villus cores (*), consistent with mild chronic villitis. (C) CD-45RO stained chorionic villi with easily identifiable lymphocytes noted within many villus cores (*), consistent with moderate chronic villitis. (D) CD-45RO stained chorionic villi with confluent lymphocytes noted within the majority of the villus cores, consistent with severe chronic villitis.

Table 1 Details of the four dizygotic twin pregnancies.

Case	Maternal age (years)	Gestation (weeks)	Sex	Birth weight (g)	%ile	Wt. diff (g)	%Wt. diff*	Placental weight (g)**	%ile	IUGR	Villitis	Outcome
1	41	36	F	1640	1	675	29	450	48§	Yes	Severe	Survived
			M	2315	30			470	52§	No	Mild	Survived
2	47	33	F	1006	0.1	821	41	340	25§	Yes	Severe	Survived
			M	1985	55			600	99§	No	None	Survived
3	31	36	M	1890	10	390	17	790	45†	Yes	Severe	Died
			F	2280	28					No	Mild	Survived
4	32	37	M	2250	15	260	10	987	80†	No	Moderate	Stillborn
			M	2510	30					No	Mild	Survived

*(Difference in birth weights/larger twin weight)×100.
**All placentas were dichorionic. (Blood groups of twins in case # 4 were different).
Two weights represent a non-fused placenta, a single weight measurement represents a fused placenta.
§Percentile from Pinar et al. [31] singleton graph.
†Weight of fused placenta, percentile from Pinar et al. [31] twin graph.

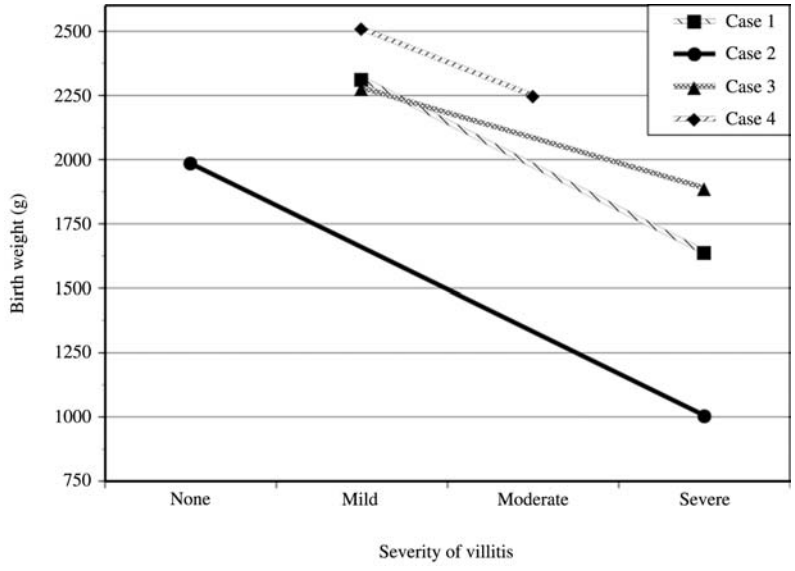

Figure 2 Birth weight as a function of degree of chronic villitis in twin pairs. Each pair of points and connecting lines represents one twin pregnancy with the birth weight of each twin plotted against the degree of chronic villitis in the placenta from that twin. All pairs show a decreased birth weight of the twin associated with the placenta with the greater degree of chronic villitis.

vascular coagulation after birth without any evidence of infection.

The discordance of chronic villitis seen in these dizygotic twins became obvious when we examined the junction between the fused dichorionic placentas using immunohistochemistry for T-cells (Figure 3). Whereas chorionic villi from the smaller twin contained numerous T-cells, the villi immediately adjacent and associated with the less affected twin showed little to no infiltrating T-cells.

Discussion

We have described a series of four dizygotic twin placentas wherein one of the placentas showed markedly more severe chronic villitis as compared to the other, without evidence of viral, bacterial or protozoan infection. Therefore, we believe that these cases of chronic villitis were due to an immunological response of the mother against fetal antigens. Although we did not do any special stains to rule out infection in these particular cases, the histopathology did not show any features diagnostic of syphilis [12, 33] cytomegalovirus [12, 33], herpes simplex virus [3] or toxoplasmosis [6]. There was no histologic evidence of viral inclusions. Other investigators have also ruled out infection as a cause of chronic villitis based on histopathology and clinical criteria only [5, 30]. In addition, none of the babies had any clinical evidence suggestive of congenital infection. Serological tests for infection were negative in both mothers and babies. Since some investigators have suggested that chronic

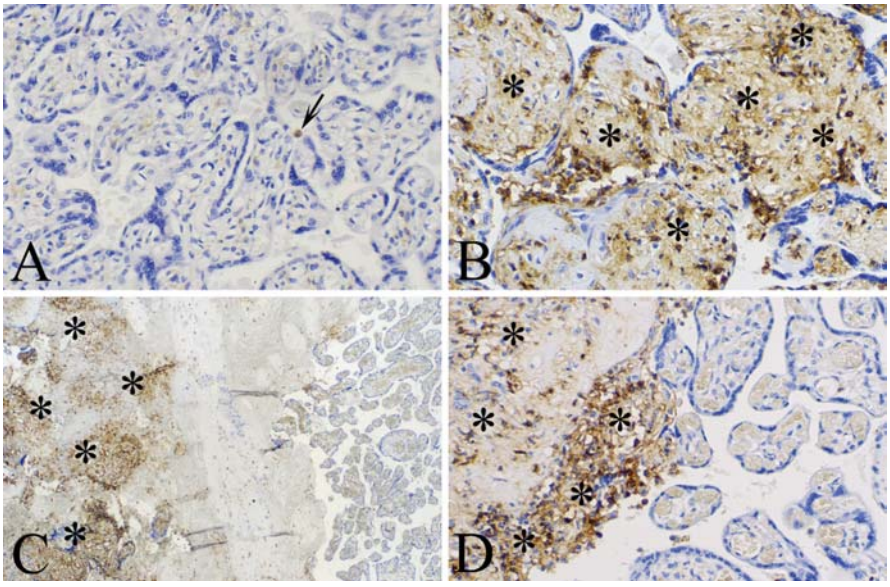

Figure 3 Immunohistochemistry for T-cells at the junction of the fused dichorionic placenta from case 3. (A) Chorionic villi from placenta of larger fetus from this case reveal only a rare T-cell within the intervillus space (arrow). (B) Chorionic villi from placenta of the smaller fetus reveals diffuse infiltration of the villus cores by T-cells consistent with severe chronic villitis. (C) Low-power view of junction between placentas shown in A and B revealing obvious T-cell infiltration on left side of junction (*) associated with the smaller twin. (D) High-power view of junction shows T-cell infiltrated villi from the smaller twin (*) directly adjacent to villi of the larger twin without any T-cell infiltration.

villitis may be due to infectious agents which are not routinely screened [6], we cannot completely rule out the possibility that these cases are the result of an obscure infectious agent. However, this possibility is made especially implausible in these twin cases since the discordances noted would have to be the result of selective infection in one placenta over the other. The complete absence of neutrophils in our series would also tend to favor a non-infectious etiology. Ernst et al. [11], using polymerase chain reaction for 16S rRNA, failed to detect any bacterial DNA in 19 cases of chronic villitis.

Whereas criteria for transplant rejection in solid organs have been well defined [4, 32], a number of investigators have compared the presence of VUE as the placental equivalent of transplant rejection with the fetus and placenta acting as an allograft against which the mother mounts an immunological reaction [16, 17, 19, 22, 24, 28, 35, 37]. Kim et al. [16] studied the immunophenotype of the cellular infiltrate in 28 cases of VUE, and demonstrated that the predominant lymphocyte was of the CD8+ type and the cellular infiltrate resembled that of transplant rejection. Labarrere et al. [24] have demonstrated the expression of intercellular adhesion molecule-1 (ICAM-1) on the surface of syncytiotrophoblast in VUE. They have suggested that this could allow maternal immune cells to adhere to fetal syncytiotrophoblast and gain access to allogenic fetal tissue. In addition, Labarrere and Faulk [22] had shown that syncytiotrophoblasts in VUE express MHC class II antigens, allowing for allogenic recognition by maternal cells. In preeclampsia, the presence of a T-lymphocyte infiltrate in the villus stroma has been taken as evidence for an immunological reaction of the mother against allogenic fetal antigens [29]. Given that our four cases did not exhibit any clinical, serological or pathological evidence of infection and the maternal environment was the same, differences in the placentas themselves are the likely triggers of the immunological response by the mother. We cannot, however, rule out the possibility that at least some cases of VUE may be due to an unidentified, obscure infectious agent.

One of the main factors affecting the incidence of chronic villitis in different series has been the number of placental blocks examined. Russel [39] examined two blocks and in this series the incidence of chronic villitis was 7.6%. Laberrere et al. [19] examined eight blocks and in their series the incidence was 26%. Other investigators have used three [15] and four blocks [18]. We believe that the examination of three blocks, as was done in our study, should identify most, if not all, cases of chronic villitis [1].

Several clinical associations have been described with chronic villitis. These include the presence of autoimmunity [7], intrauterine growth restriction [5, 7, 36] spontaneous abortion [38], recurrent pregnancy loss [36] and prematurity [7]. Two of our patients had a history of recurrent pregnancy loss and spontaneous abortions. In three of our patients, the twin with the more severe villitis was growth restricted. An interesting finding in our study was that the severity of the villitis correlated with placental weight. Unlike some other studies, we did not find any

association between chronic villitis and maternal weight [36, 40] or structural deformity of the uterus [36]. Chronic villitis in our series was also not more common in primigravidas [40].

There are several reasons for discordance in the birth weight of twins, including twin-twin transfusion syndrome, genetic differences, sex differences and twin zygosity [13]. Chronic villitis has also been described as a cause for birth weight discordance in twins [10]. Two of our twins had birth weight differences of 29% and 41%. In both cases, villitis in the placenta of the twin with the lower weight was much more severe as compared to the placenta of the twin with the greater weight. Even in the two twins where the weight discordance was $<20\%$, the severer villitis was associated with the twin of lesser weight. Since all the twin placentas examined in our series were dichorionic, twin-twin transfusion syndrome is not a possible explanation for the discordance, nor can the differences in weight be accounted for by sex differences alone [10]. VUE has been characterized as an independent risk factor for IUGR [5], thought to result from decreased placental blood flow or decreased transcription of the gluconeogenic enzyme, phosphenolpyruvate carboxylase [2, 7].

Until recently, it was generally believed that syncytiotrophoblasts formed an impenetrable barrier, preventing access of maternal cells to fetal antigens. This is no longer held to be true. The ways in which maternal inflammatory cells can access the villus stroma have been recently reviewed by Redline [35]. These include damage to the syncytium by increased apoptosis and thrombosis of maternal and fetal blood vessels, expression of adhesion molecules by the syncytiotrophoblast and entrance of maternal lymphocytes into villus stroma at sites of anchoring villi where syncytiotrophoblasts are differentiating into invasive intermediate syncytiotrophoblasts. Cytokines may be involved in these processes [7, 35]. During normal pregnancy the maternal immune response is shifted to the Th-2 type response, which is more closely related to humoral immunity. In contrast, the Th-1 type response, which is more closely related to delayed type hypersensitivity, is suppressed [41]. A mouse model of spontaneous abortion exists where mating between two specific mouse strains (DBA/2 and CBA/J) results in a Th-1 response with deleterious effects on the pregnancy. This Th-1 response can be reversed by manipulation enhancing the Th-2 response [9]. Cytokines produced by the Th-1 response include mainly tumor necrosis factor-α (TNF-α), tumor necrosis factor-β, interferon γ (IFN γ) and interleukin (IL) 2, while cytokines produced by the Th-2 response include IL 4, 5 and 10. It has been demonstrated that the peripheral blood mononuclear cells in mothers with unexpected recurrent abortions produce Th-1 type cytokines [14]. Both TNFα and IFNγ diminish trophoblast differentiation and enhance apoptosis [43]. In addition, they also enhance the expression of the adhesion molecule ICAM-1 on trophoblasts [42]. As discussed earlier, syncytiotrophoblasts in areas of VUE express ICAM-1 [24]. It is possible that chronic villitis may represent an aberrant immunological response to trophoblast antigens, causing a shift of the maternal immune response away from the Th-2 type to the Th-1 type response. The increased production of both TNFα and IFNγ may help maternal lymphocytes gain access to the fetal compartment by enhancing the expression of ICAM-1 to which the maternal lymphocytes can attach. However, the nature of the antigen eliciting this response has yet to be determined [7]. Similarly, enhanced levels of TNFα and IFNγ can result in apoptosis and decreased differentiation of trophoblasts, both of which are associated with IUGR and recurrent abortion [8, 25]. A recently described mechanism of immunological tolerance of the mother towards the fetus involves tryptophan metabolism [26, 27]. Recently Nishizawa et al. [29] have described decreased mRNA expression and enzyme activity of indoleamine 2,3-dioxygenase (IDO) in placentas of women with preeclampsia. In their study, IDO activity correlated inversely with blood pressure. Also T-cell infiltration in villus stroma was observed to be reciprocally proportional to IDO activity. They have ascribed this as an immunological reaction of the mother against an allogenic fetus.

In summary, we described a series of patients with chronic villitis without any evidence of infection. Most intriguing is the discordance of chronic villitis seen in these dizygotic twin placentas which suggests that analysis of these types of cases may help to elucidate the triggering mechanism for maternal immunologic rejection of the placenta. Maternal immunologic rejection should be considered in all cases of IUGR, spontaneous abortions, recurrent pregnancy loss and birth weight discordance in twins.

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