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Review

Chronic villitis of unknown etiology

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Abstract

The diagnosis of chronic villitis of unknown etiology (CVUE), characterized by focal areas of inflammation with mononuclear cells and areas of fibrinoid necrosis in chorionic villi, can only be set-up after exclusion of a latent maternal-fetal transmission of infectious agents by sophisticated techniques such as polymerase chain reaction. Significant associations of CVUE with maternal body mass index, multigravidity and ethnicity were reported. While a fetal origin of the inflammatory cells has been evoked, there are many more arguments drawn from histopathology and immunohistology for a maternal immune response against the foreign fetal allograft. CVUE is detected in 7–33% of placentas, mainly after idiopathic intrauterine growth retardation, unexplained prematurity, preeclampsia, perinatal asphyxia and intrauterine fetal death. CVUE is also more frequent in pregnancies affected by autoimmune or alloimmune diseases. Considering the high rate of recurrences after an index case of CVUE, we would suggest to associate aspirine and corticosteroids in further pregnancies, a regimen that was successful in our experience but must be confirmed by other studies. The same is true for the alleviated inflammatory immunologic response recently obtained by a weekly use of maternal intravenous immunoglobulins.

Keywords: Chronic villitis of unknown etiology; Pregnancy complications; Recurrences; Prevention

Contents

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1. Introduction

Chronic villitis is characterized by focal areas of inflammation with mononuclear cells and areas of fibrinoid necrosis in chorionic villi. Inflammatory patterns of chronic villitis include lymphohistiocytic, lymphocytic, lymphoplasmocytic lesions, and granulomatous inflammation with multinucleate giant cells [1–5] (Fig. 1). The percentage of placentas with chronic villitis is reported as being 7, 6–10% in the United States [1,3], 13.6% in the United Kingdom [2], 14.2% in New Zealand [5] and up to 33.8% in Argentina [4]. These widely differing incidences have been attributed to three factors, the adequacy of tissue sampling, the stringency of histologic diagnostic criteria, and the population from which the placentas were obtained. As shown by Redline et al. [6], and Beebe et al. [7], kappa values for lesions of distal villi such as stem villitis and avascular villi are generally superior than for large vessel thrombi with reduced uterine blood flow states (range 0.65 −0.83 versus 0.34–0.40). The current reliability in assessing chronic villitis shows intra-observer agreement in 84.7% and inter-observer agreement in 81% [8]. In the experience of Sun et al. [9], underdiagnoses of chronic villitis, identified on review but not mentioned in the original report, were 21.7%.

After the use of sophisticated techniques as polymerase chain reaction (PCR), eliminating the possibility of materno-fetal transmission by rubella [1], enterovirus [1], varicella [10], toxoplasmosis [10], syphilis [11] nonsyphilitic spirochetosis [12] and cytomegalovirus [13], in more than 90% of the affected placentas, the causative agent was neither clinically, nor pathologically apparent suggesting the occurrence of chronic villitis of unknown etiology (CVUE) [2]. In fact, Ernst et al. [14] found no demonstrable product of infection from 19 specimens of placentas with multifocal chronic villitis using a polymerase chain reaction (PCR) with primers for the universal bacterial 16S RNA DNA which is sensitive down to approximately 1500 bacteria per specimen.

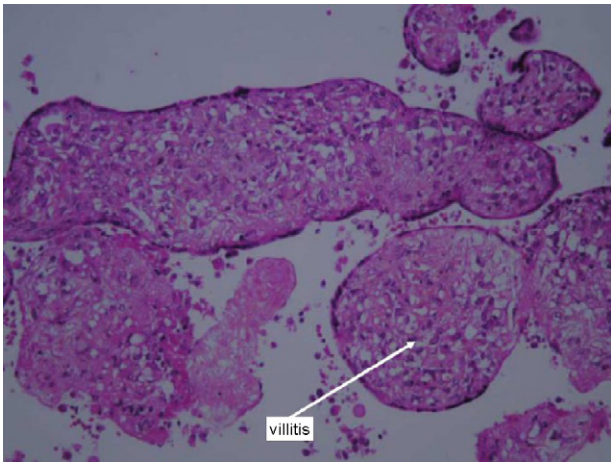

Fig. 1. Chronic villitis of unknown etiology. The mononuclear infiltrate concerns the villous stems. (Hematoxylin and eosine, original magnification 200×.)

Frequent encountered accompaniments of CVUE include fetal villous thrombosis, villous vascular obliteration, hemorrhagic endovasculopathy (vascular obliteration with enmeshed fragmented red cells), villous stromal sclerosis and chorangiosis [15,16].

The boundary of CVUE with massive chronic intervillositis of unknown etiology is not clearly defined. From six cases where this lesion characterized by fibrinoid and trophoblastic necrosis with massive infiltration of the intervillous space by mononuclear cells was observed, five fetuses were affected by intrauterine growth retardation and one by sudden intrauterine death. Considering that four out of these six patients had associated CVUE, Labarrere and Mullen [17] speculated that chronic intervillositis may represent an extreme variant of CVUE. In the experience of Boyd and Redline [18] from 31 cases of chronic histiocytic intervillositis without inflamed villi, diagnosed after recurrent spontaneous abortions, repetitive intrauterine growth retardations and intrauterine fetal deaths, the prognosis was also very pejorative since the overall perinatal mortality rate was 77% and only 18% of pregnancies could reach 37 weeks' gestation.

2. Pathophysiology

An immunological origin for CVUE was initially evoked by Labarrere and Althabe [19] because the lowest values of circulating complement CH50 could be found in nulliparous women with placental chronic villitis associated with small-for-gestational age infants (SGA). The same authors [20] tested sera from 22 women and their singleton full-term infants for inhibition in one-way mother/father mixed lymphocytes culture (MLC), and the results showed evidence that blocking factors capable of inhibiting responses of wife's lymphocytes to husband's cells in MLC were absent in sera of women with SGA infants associated with CVUE in 6 out of 10 cases, while there were present in 12 normal pregnancies when infants were adequate for gestational age (AGA).

- Demonstration of the immunological origin of inflammation with the use of immunohistologic techniques and monoclonal antibodies.

  Labarrere et al. [4] found that macrophages were the most common cells involved in CVUE. They were apparently activated because they expressed class II major histocompatibility complex antigens [21]. In the same lesions, many T cells of the helper phenotype were identified, while suppressor T cells and monocytes were few and B cells were not identified. Macrophages may be activated by cytokines released from antigen-activated CD4-reactive T lymphocytes. It is not known what triggers these immunologic events, but the presence of villitis in normal placentas suggests that the causative factor is present in every pregnancy [4]. Furthermore,

tissue factor-like procoagulant activity of endothelium is markedly increased by interleukin-1 and other cytokines [4]. This mechanism is amplified by down-regulation of thrombomodulin and secretion of platelet-activating factor. The most obvious aspect of coagulation in CVUE is the perivascular and trophoblastic basement membrane deposition of factor IX and the presence of fibrin. Platelets are also involved. The result is an endothelial lesion measured by loss of factor VIII von Willebrand from the damaged cells with outflow into the circulation. If fetal stem vessels are not functional, avascular necrotic changes in affected villi might be expected to be infiltrated with macrophages to clear away debris [4].

- CVUE and major incompatibility of tissue antigens.

  At histologic examination of placentas from donor oocyte IVF pregnancies, a situation of total incompatibility between mother and fetus, Perni et al. [22] found significantly more chronic villitis ($p < 0.001$) and chronic deciduitis ($p = 0.03$), without decidual vasculopathy than in placentas of non-donor cycles.
- Origin of the inflammatory cells.

  The opinion from Altshuler and Hyde [1] is that CVUE is not primarily a manifestation of graft rejection because they never encountered it with first trimester fetuses who lack immunocompetence and because morphologic evidence of a *fetal response* to foreign antigen was best seen in early villitis wherein inflammatory cells appear to be migrating from fetal capillaries to the villous trophoblastic surface.

But, by in situ hybridation using X and Y chromosome-specific probes and by immunostaining for CD3 and CD45 on CVUE placentas from male infants, it was obvious for Redline and Patterson [23] that the proportion of *maternal cells* within each placental focus was significantly correlated with the number of CD3-positive T lymphocytes, suggesting that they crossed the materno-fetal barrier. Moreover, by using a double antibody technique involving monoclonal antibodies to HLA-DR and HLA-DRw52 antigens, Labarrere and Faulk [24] showed unequivocally that cells in areas of placenta immunopathology were predominantly of maternal origin.

The presence of maternal hematopoietic cells (CD3+ and CD19+), widely distributed in fetal liver, lung, heart, thymus, spleen, adrenal gland, kidney and placenta was also documented at autopsy in a second-trimester fetus with malformations [25] and the cells passing from maternal into fetal circulation were shown to result in a chimerism associated with human auto-immune diseases, such as juvenile dermatomyosis and idiopathic inflammmatory myopathies.

3. Predisposing factors of CVUE

After a multivariate analysis in the category of SGA infants performed by Bercroft et al. [5], CVUE had significant associations with maternal prepregnancy body weight and body mass index ($p = 0.04$), a situation known to lower the immune function. Similarly, Redline and Abramowsky [26], reported that out of 10 mothers presenting recurrent villitis, 5 were obese, in comparison with no maternal weight excess in 20 cases of nonrecurrent villitis with less severe fetal effects. The correlation of CVUE with multigravidity ($p = 0.03$) is consistent with enhancement of immune response from repeated exposure to fetopaternal antigens, as is the increasing severity of recurrent CVUE. After delivery of SGA infants, CVUE was also related to kidney or urinary problems during pregnancy ($p = 0.05$) and to ethnicity ($p = 0.03$) with a low incidence in Maori, Chinese and Indian populations [5].

4. Clinical implications of chronic villitis of unknown etiology

4.1. Intrauterine growth retardation (IUGR)

In 44 placentas of SGA infants, Labarrere et al. [27] found that CVUE was present in 86% of placentas with 10% of villi being inflamed, while respective values in placentas of 19 normal AGA infants were 26 and 1.2%. Commonly, 24–31.5% of idiopathic IUGR may be attributed to CVUE [28–30].

In a study by Althabe and Labarrere [31], concerning 211 placentas, a higher incidence of chronic villitis and inflamed villi was observed as the average birthweight decreased in cases with normal as in cases with low ponderal index (PI), the highest incidence being found in placentas from infants with harmonic or symmetric growth retardation (normal PI), suggesting an early and more severe maternal immunological reaction to fetal tissues. The same results were reported by Salafia et al. [32] with severe chronic villitis in 6.3% of symmetric growth retarded infants, versus 0% in asymmetric ones and 1.5% in AGA infants ($p < 0.001$).

In 249 singleton very low birthweight infants (<1.500 g), IUGR was associated with chronic inflammation, and was independent of decidual vasculopathy, while in the presence of maternal hypertension IUGR was directly related to aberrant conversion of spiral arteries and decidual vasculopathy [33]. In a study conducted at Auckland by Becroft et al. [5], CVUE was an independent risk factor for SGA (adjusted OR: 2.35 (95% CI: 1.55–3.56), while villitis in conjunction with maternal hypertension increased the risk of SGA substantially (adjusted OR: 17.7 (95% CI: 3.6–86.9).

The severity of the fetal growth restriction may result all together from the number of inflammatory lesions and from histopathologically evidence of low placental blood flow, but a possible reduction in phosphoenolpyruvate carboxykinase transcription by cytokines altering the gluconeogenic metabolism of SGA infants warrants further investigation [1].

4.2. Twin pregnancies

Twins with rare foci or diffuse placental involvement by CVUE had a lower mean birthweight than their cotwin with less or no chronic inflammation [34]. Similarly, in dichorionic discordant twins, Eberle et al. [35] observed that chronic villitis was present more frequently in the light twin (16.7%) than in the heavy one (5.6%), a finding that was not true for monochorionic twins.

4.3. Idiopathic prematurity

Chronic villitis was observed in 4% of placentas examined after delivery between 22 and 28 weeks' gestation, 9–14% between 29 and 32 weeks' gestation and 16–44% between 33 and 36 weeks' gestation [29,36]. An explanation for the rarity of chronic villitis in early preterm pregnancies may be related to the immaturity of placental macrophages.

Chronic inflammation was significantly more frequent in preterm deliveries without signs of acute inflammation than in those cases with umbilical vasculitis which reflected acute ascending bacterial infection (17% versus 8%, $p < 0.05$) [36].

4.4. Autoimmune diseases

Labarrere et al. [37] investigated the presence of CVUE in 18 placentas from 15 mothers with several autoimmune diseases including systemic lupus erythematosus, idiopathic thrombocytopenic purpura, autoimmune thyroid diseases and multiple sclerosis and they detected more maternal vascular lesions and CVUE (61%) than in the control group (11%). Comparing the placentas delivered at more than 18 weeks' gestation in treated antiphospholipid (APL) antibodies syndrome, excessive perivillous coagulation, avascular terminal villi and chronic villitis/uteroplacental vasculitis tended to be more common than in only serological APL cases ($p = 0.07$) [38]. While the presence of APL antibody largely, but not invariably, predicts fetal death, antiphospholipid antibody-independent chronic villitis may represent a second mechanism of systemic lupus erythematosus-related change [39].

4.5. Alloimmune diseases

De Tar et al. [40] described a case of neonatal thrombocytopenia and CVUE associated with microthrombi that were supposed to be due to paternal lymphocyte traffic and further HLA-sensitization. The production of autoantibodies to paternal antigens, mainly HLA alloantibodies, has been shown to mediate platelet aggregation in blood and the binding of HLA class I antibody to the endothelial cells may result in cytokine-mediated endothelial injury and subsequent release of tissue factor with activation of the coagulation.

Althaus et al. [41] detected 83% of CVUE in placentas associated with neonatal allo-immune thrombocytopenia consecutive to fetal platelets destruction by maternal antibodies against fetal platelet antigens, while no placenta in patients treated by intravenous immunoglobulin (IVIG) displayed this condition, so that it may be speculated that weekly maternal IVIG (1 g/kg) alleviated the inflammatory immunologic response.

4.6. Hypertensive pregnancies

Labarrere and Althabe [42] considering 146 placentas from mothers with pregnancy-induced hypertension and a normotensive control group of 215 cases, concluded that a statistically significant higher incidence of villous lesions (60% versus 25%) and more inflamed villi (6.6% versus 1.8%) were observed in placentas of hypertensive mothers when infants were over the 25th centile of the ponderal curve. In a further study, CVUE was found in 25% of control placentas after normal pregnancies, 26% of placentas from chronic hypertension without preeclampsia, and mainly in 80% of placentas from chronic hypertension with superimposed preeclampsia [43]. In a review of 76 cases of preeclampsia in singleton live-born nonanomalous infants born at 22–32 weeks' gestation, Salafia et al. [44] identified more frequently CVUE in preeclampsia than in 353 cases of spontaneous prematurity (20% versus 3%; $p < 0.001$), suggesting that immunopathologic processes and coagulation disorders may also be involved in the pathophysiologic mechanisms of preterm preeclampsia independently from the classical uteroplacental vascular pathologic features.

4.7. Perinatal asphyxia

From a retrospective study about 431 preterm deliveries occurring between 22 and 32 weeks' gestation, Salafia et al. [45] observed that chronic villitis was associated with a reduction in umbilical artery for pH ($p < 0.05$) and P_{O_2} ($p < 0.001$) and with an increase in P_{CO_2} ($p < 0.05$).

Routine histological examination of the placenta following a perinatal death provides a necessary add-on in autopsy examination, as it gives essential information on the cause of death and therefore helps in planning a future pregnancy and triggers a more effective prenatal monitoring. The cause of cerebral palsy being clearly documented in less than 10% of cases, the placenta is an important potential means of establishing that fetal damage may cause bad pregnancy outcome independently of clinical care. In fact, in a first series of 40 cases term infants with neurologic impairment following term birth drawn from a database containing clinicopathologic data derived from the medicolegal consultation files compared with placentas from 176 consecutive meconium-stained term infants at low risk for cerebral palsy, Redline and O'Riordan [46] found that diffuse CVUE had an unadjusted OR at 4.1 [1,3–13] for neurologic impairment and that extensive avascular villi

which have often CVUE as a possible underlying cause had an adjusted OR at 9.0 [1,6–51] for developmental brain abnormalities believed to occur well before labor.

In a further report, Redline [47] compared the placentas of 125 neurologically impaired term infants who were the focus of clinical negligence litigation and 250 consecutive singleton deliveries of more than 36 weeks of gestation and showed that from four severe concomitant lesions like fetal thrombotic vasculopathy, chorioamnionitis with severe fetal vasculitis, meconium-associated fetal vascular necrosis and chronic villitis with obliterative fetal vasculopathy, the later was found in 18% of index cases versus 3% of the comparison group ($p < 0.0001$). Similarly, in a group of 43 neonates with electrically confirmed seizures in the immediate neonatal period, chronic villitis was one lesion considered more likely to have an antepartum association, in conjunction with abnormal villous maturation and infarction [48].

5. Recurrences

CVUE has been associated with recurrent pregnancy complications. In ten cases with repeat IUGR, recurrent CVUE with a high incidence of inflamed villi was described by Labarrere and Althabe [49] in both first and successive pregnancies, confirming that CVUE is due to a maternal immune response to placental antigens and that subsequent pregnancies with the same father might be similarly affected, a situation radically different from preeclampsia, where incidence decreases with further gestations from the same husband. In the series of Redline and Abramowsky [26], IUGR was seen in 18 out of 41 pregnancies with recurrent villitis, an incidence markedly greater than the two cases of the control group of 82 pregnancies without recurrence ($p < 0.01$).

Russell et al. [50] reported the observation of a patient whose five successive pregnancies ended in four unexpected third-trimester deaths in utero and only one live birth with IUGR at 37 weeks' gestation. The placentas of the last three pregnancies showed marked focal chronic parenchymal inflammation with wide spread necrosis, villous vasculitis and a lymphocytic deciduitis of the maternal floor. The poor prognosis of CVUE recurrences was confirmed by Redline and Abramowsky [26] in a retrospective study showing that for 10 patients with recurrent villitis in 41 pregnancies the reproductive loss was of 60%, while in a control group of 20 patients with non recurrent villitis and 82 pregnancies the perinatal loss was only 37%.

Chronic villitis of unknown etiology is a placental abnormality that often coexists with hemorrhagic endovasculitis, a lesion which was associated with stillborn infants in 64.3% of cases and with a recurrence rate of 28.9% in a series of 97 women collected by Sander et al. [15]. Higher rates of recurrence were found with progressively increasing severity scores for the first referral chronic villitis ($p < 0.02$).

6. Prevention of recurrences

CVUE being essentially an immunological process, corticosteroids should be administered in order to prevent or reduce the deleterious chronic villous inflammation in further pregnancies. Seeing that the chronic infiltrate is preferentially of maternal origin, we preconize prednisone, 20 mg/day from the early second trimester, rather than a corticosteroid which may cross the placental barrier such as betamethasone or dexamethasone. Due to the frequent association of CVUE with villous obliteration and thrombosis, it seems logical to prescribe simultaneously aspirin 100 mg/day from 12 until 35 weeks' gestation. We have now treated preventively five patients with a history of recurrent CVUE by using this protocol and we obtained four living infants. The only failure attested by an intrauterine fetal death at 16 WG was associated with severe chronic intervillositis.

The recent favourable effect of intravenous immunoglobulins reported by Althaus et al. [41] is another interesting perspective.

7. Conclusions

During pregnancy, there are no specific patterns suggesting CVUE, although chronic inflammation of the placenta may be seen via somewhat higher levels of hCG and a significant raise in alpha-fetoprotein in the early second trimester, then by fetal growth restriction and abnormal nonstress testing [29], and in our experience by a heterogeneous placental pattern at sonography with focal sonolucent areas [51].

Yet it must be remembered that CVUE is only diagnosed after histopathologic examination because there is no particular macroscopic pattern, unless a weight deficit not greater than 2S.D. below the mean [29]. So, it may be appropriate to store all placentas for at least 72 h, a delay during which most severe neonatal complications may have arisen. If the infant develops neurological symptoms or requires unexpected admission to a neonatal intensive care unit then placental examination may reveal an important etiological factor such as CVUE.

The preventive effect on recurrences by combining corticosteroids and aspirin is to be confirmed.

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