Combining corticosteroid and aspirin for the prevention of recurrent villitis or intervillositis of unknown etiology.

G. Boog*, C. Le Vaillant*, F. Alnoukari*, F. Jossic**, J. Barrier***, J.-Y. Muller****

* Service de Gynécologie-Obstétrique, CHU de Nantes, 38, boulevard Jean-Monnet,

44093 Nantes Cedex 1.
** Service d'Anatomie et Cytologie Pathologiques, CHU de Nantes, Hôtel Dieu, 30, boulevard Jean-Monnet, 44093 Nantes Cedex 1.
*** Service de Médecine Interne, CHU de Nantes, Hôtel Dieu, 30, boulevard Jean-Monnet, 44093 Nantes Cedex 1.
**** Service d'Immunologie, CHU de Nantes, 9, quai Moncousu, 44093 Nantes Cedex 1.

*This is an English translation of made from the original paper in French entitled « **Association des corticoïdes à l'aspirine pour la prévention des récidives de villite ou d'intervillite chroniques d'étiologie indéterminée** »*

We report the cases of two patients who had a favourable outcome with aspirin and corticosteroid therapy during pregnancy for chronic villitis of unknown etiology complicated by labor asphyxia and further intrauterine fetal demise in one gravida 3 patient and for chronic intervillositis of unknown etiology diagnosed after three perinatal deaths in another patient (gravida 4). Chronic villitis of unknown etiology (CVUE) is detected in 7 to 33% of placentas, mainly after intrauterine growth retardation (IUGR), unexplained prematurity, preeclampsia, perinatal asphyxia and intrauterine fetal death (IUFD). The less frequent chronic intervillositis of unknown etiology (CIUE) (0.6 to 0.9/1.000) has been implicated in recurrent severe pregnancy complications, such as spontaneous abortions, IUGR and IUFD. Histopathology and immunohistology are in favour of an immune response against the foreign fetal allograft. The favourable results obtained with corticosteroids and aspirin remain to be confirmed by larger series.

Inflammatory lesions of chronic placental villitis are found in varying proportions according to the sample groups studied and the number of specimens taken from the sample tissue presented for analysis. The figures vary from 10 to 33% in placentas collected after high-risk pregnancies, 11.7% after the birth of children of normal weight and 7.6 to 14% of placentas in the study population [1-5]. Macroscopically, there is no specific symptoms, outside of a discrete placental hypotrophy.
The histopathology is that of a mononuclear infiltrate involving lymphocytes, plasma cells and histiocytes [2]. The lesions are accompanied consistently a thrombosis of the villous trunks, endovascularite colitis, sclerosis of the chorion and chorionic angiose villus [1, 2]. Amongst these villi lesions, some have obvious etiologies associated with maternal-fetal infections. In other cases, when all the tests for the trans-placental transmission of infectious agents were negative, some authors introduced the term "chronic villitis of unknown etiology" (CVUE) [1-8] .

Other authors have shown many more rarely chronic inflammatory patterns on the maternal side of the placenta, the intervillous space, with or without an extension onto the fetal side. *Chronic intervillositis of unknown etiology* (CIUE) also known as *massive chronic intervillositis* (MCI) or *chronic histiocytic intervillositis* (CHIV)] is a much rarer entity of unknown origin, recently identified by Labarrere and Mullen [8]. In this disease, lesions are predominantly in the placental intervillous space. These lesions are characterised by

Translated by CAABelardo

mononuclear inflammatory infiltration of maternal origin including monocytes, histiocytes and lymphocytes with both villous and intervillious fibrinoid deposits and sometimes aspects of chronic villitis. It can be a massive infiltration or localized to the intervillous chamber.

On the occasion of two clinical cases, we discuss the prognosis of CVUE and CIUE and preventive therapeutic possibilities.

DESCRIPTION OF CLINICAL CASES
Case 1: Chronic villitis of unknown etiology (CVUE)

Mrs C., 32 years old. She weighs 70kg and measures 1.58m. She has a diabetic mother. She was hospitalised at 35 weeks of gestation (WG) for induction of labor due to abdominal growth arrest and on ultrasound, fetal oligohydramnios in a context of her previous history:

- In 1996, she underwent a Caesarean section at 40 weeks during labour because of late decelerations of fetal heart rate with small oscillations, less than 5 beats per minute. The female child, weighing 2780g, had an APGAR score of 6 at 1 minute and 10 at 5 minutes, with a favourable neonatal outcome. The umbilical arterial pH was 7.29. Hypotrophic placenta of 385g (normal 490g) displaying lesions of monocyte macrophage villitis;

- In 1998, which did not receive any particular treatment, it was presented for a stillbirth at 37 weeks, despite a satisfactory clinical course. After a labour triggered by three tablets of Mifepristone, she delivered a boy of 2300g, macerated. On examination of the placenta, it was also hypotrophic, weighing 282g (average 450g), the same lesions of chronic villitis were found that had presented during the previous pregnancy (Fig. 1).
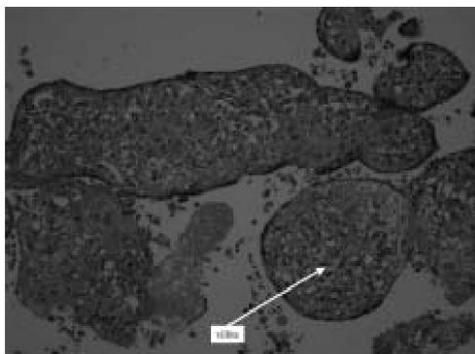

Figure 1. *Chronic villitis of unknown etiology. The mononuclear inflammatory infiltrate concerns the villous stems (hematoxylin and eosin, original magnification 200⬚⬚).*

The immunological assessment made it possible to exclude any classic autoimmune disease, but found, at the histocompatibility class I in maternal antigens A23, A24 and B44 and in the father's antigens A2, B7 and B40. Moreover, anti-HLA IgG antibodies were detected in the mother's serum, directed mainly against the structures of Class I, but also Class II exceptionally high strength, higher than 1/100th with very broad anti-paternal characteristics (B7 and B40), without auto-reactivity;

- In 2002, the patient was treated from the 12th week by Betamethasone at a dose of 2 mg/day and 100 mg of aspirin/day. At 16 weeks, the beta-hCG was 0.27 MoM and alpha-fetoprotein at 1.12 MoM. At 22 weeks, the uterine Doppler velocimetries were normal. Gestational diabetes required insulin therapy. Another Caesarean section was performed at 35 weeks due to a failed induction. The male infant weighing 1600g had an APGAR score

10 at 1 and 5 minutes of life, with an umbilical arterial pH of 7.20. Its development was favorable. Pathological examination of the placenta, weighing 206g (average 425g), aspects of lymphocytic infiltrate or macrophage of the chorion villus were again detected, but less marked than in the previous pregnancy.

Case 2 : *Chronic villitis and intervillositis of unknown etiology*
Mrs. S., 36 years old. She weighs 48 kg and measures 1.56m. She is a non-smoker. It has no noteworthy family medical history nor any personal conditions, medical or surgical. She was hospitalised at 24 weeks for fetal monitoring of her 4th pregnancy, due to an especially complex obstetric history. The three previous pregnancies had ended in perinatal death:
- In 1999, she gave birth to a stillborn child at 31 weeks, weighing 1153g, female. The report showed the presence of anti-HLA antibodies specific to the father. The placenta weighing 156g, below the 10th percentile, the cross section presented multiple infarcts of varying size. The histopathological report did not indicate acute nor chronic inflammation.
- In 2000, she was hospitalized at 29 weeks because of fetal ascites. Fetal blood analysis indicated that there was an anemia of 6g/dL of hemoglobin, requiring an immediate in utero transfusion. An emergency caesarean section was performed immediately afterwards, due to severe abnormal fetal heart rate, but the child died shortly after blood tests indicated significant thrombocytopenia. The placenta, weighing 420g, was the site of a hematoma, but, histologically, there were no other significant lesions.
- In 2002, she was followed for the first time in our department. A thrombophilia was performed which showed only a heterozygous mutation of the gene for Methylenetetrahydrofolate reductase (MTHFR). She received preventive treatment with aspirin 100 mg / day. Monitoring of pregnancy showed a chorionic gonadotrophin (hCG) at 0.60 MoM and an alpha-fetoprotein of 1.42 MoM at 15 weeks. There was a slight increase in the resistance index of both uterine arteries to 0.62 without protodiastolic markers. While fetal growth was around the 50th percentile on ultrasound, and the umbilical resistance index was 0.62, the child died suddenly in utero at 23 weeks. Its weight was 433g (between 10th and 25th percentiles on the AUDIPOG charts) and it was not malformed. The examination of the placenta showed, however, quite marked lesions of chronic villitis and intervillositis and resembling an immunological conflict (Fig. 2);
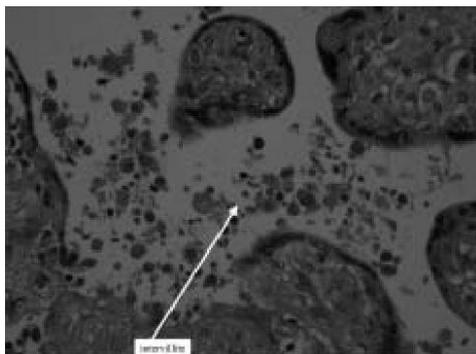

Figure 2. Chronic intervillositis of unknown etiology. The inflammatory pattern includes lymphohistiocytic and lymphocytic cells predominantly in the intervillous chamber of the placenta (hematoxylin and eosin, original magnification 400 ·).

- In 2005, she was hospitalized at 25 weeks due to previous history for daily fetal heart rate monitoring supervision by the fetal heart rate. Previously, the hCG was 1.41 MoM and to the alpha-feto-protein at 1.32 MoM at 16 weeks. At 22 weeks the Doppler velocimetries of uterine arteries were abnormal with resistance index respective to 0.72 and 0.77 and bilateral protodiastolic markers. Aspirin had been started from 12 weeks at 100 mg/day. Given the histological appearance of the placenta during pregnancy noted earlier (2002), an urgent immunohistochemical study was undertaken urgently which showed an

abnormal cell population mostly made of comprising of histiocytic-macrophage CD 68+ cells which mingled with quite a few CD3+ lymphocytes corresponding to T-Lymphocytes. Subtyping of T-Lymphocytes showed a moderate number T-Lymphocytes CD8+ and a few CD4+.

A study of the couple's HLA system was undertaken, which identified:

- In the mother, in Class I phenotypes A3, A11 and B44 and Class II phenotypes DR13, DR16, DQ5 and DQ6;

- In the husband, in Class I phenotypes A2, B27 and B44, and in Class II phenotypes DR4, DR7, DQ2 and DQ7;

- The test for anti-HLA IgG antibodies of paternal origin was carried out in the mother who was found to be 100% positive for Class I and 91% for Class II. The presence of paternal anti-HLA and histology suggestive of placental pathology of immunological order prompted us to start a cortico-therapy Prednisone, 20 mg/day, from that hospital. The pregnancy was then continued as normal, with fetal growth in the limit of 10th percentile and a satisfactory umbilical Doppler velocimetries (IR = 0.64). Given the low cross-placental passage of prednisone, an acceleration of fetal lung maturity was established by two intramuscular injections of betamethasone, 2x12 mg 24 hours apart.

Amniocentesis for fetal maturity was conducted at 32 weeks and a karyotype check conducted in situ hybridization (FISH), eliminating the possibility of trisomy 13, 18 and 21. Given the result in the P/S (palmitic acid / stearic acid) to 6.5 (threshold of maturity to 5), an iterative cesarean section was performed, allowing the extraction of a girl of 1370g (25th percentile of per- AUDIPOG curves), with an APGAR score at 5 to 10 minutes and an umbilical arterial pH of 7.28. The evolution of the child in neonatology was quite satisfactory. Examination of the placenta displayed again as being very hypotrophic 200g (normal 360g), again showing infarction cutting off about 20% of the placental surface, but no villitis and intervillositis lesions.

DISCUSSION

Chronic villitis of unknown etiology

The notion *"chronic villitis of unknown etiology"* (CVUE) was originally discussed by Altshuler and Hyde [1], Russell [7] and Labarrere et al. [8]. This diagnosis can only be used when a thorough etiologic investigation was performed to exclude a maternal-fetal transmission of various infectious agents, often with sophisticated techniques such as PCR: rubella, enteroviruses [1], varicella [9, 10], toxoplasmosis [9], syphilis [11, [12], cytomegalovirus [13], non-syphilitic spirochetosis [14].

Chronic inflammatory lesions of CVUE may be associated with impaired membrane form of chronic chorioamnionitis or the intervillous space, giving an appearance of chronic intervillitis [15, 16]. Recognising the difficulty of diagnosis, Redline et al. [17] showed that the reproducibility of diagnosis was greater for distal placental lesions, such as CVUE, with inflammation of the villous core and avascular villi (kappa 0.65), more easily recognized as thromboses of large vessels (kappa 0.34). In the experience of Khong et al. [18] the consistency of diagnosis CVUE for the same observer was 84.7% and for different observers of 81%. Diagnostic accuracy obviously depends also on the number of cuts made on the same placenta.

Translated by CAABelardo

Pathophysiology of chronic villitis of unknown etiology
Major works were carried out by Labarrere et al. [19-25]. From the outset, these authors
suggested a deficiency of blocking antibodies, which are able to inhibit the immune
response of the mother against the paternal antigens, and thus protect against the
allograft rejection of pregnancy [19-21]. They were continually evident, in the case of
chronic villitis, in the maternal complemented by a decrease in CH50 [22] and in the
immunocytology, the presence of antibodies against the histocompatibility antigens HLA-
DR [23] and stimulation of helper T- lymphocytes which, through macrophages, the trigger
clotting process and alteration of the vascular endothelium [24, 25].

However, it is not clear whether the inflammatory cells seen in the villous axes are
maternal or fetal. For Altshuler et al. [1], it was mostly fetal cells, because the histological
features of CVUE are identical to those of the fetal response to chronic infection, even
though CVUE did not appear before the presence of immunocompetent cells in the fetus,
that is to say after the first trimesters, the two trophoblastic layers normally oppose the
passage of maternal cells, in early villite chronic inflammatory cells are visible in their
migration to the surface of trophoblastic cells than of maternal origin are identified only in
very advanced lesions CVUE and the pathologies associated with an important passage of
fetal antigens, such as allo-immunization, did not accompany CVUE lesions.

For other authors, it is an immune inflammatory reaction of maternal origin, present in all
pregnancies, in reaction to the release into the general circulation of debris associated
with apoptosis and renewal of trophoblastic villi. It was during this apoptosis as solutions
of continuity in both trophoblast layers allow the passage of maternal cells in the villi [3,
26]. In fact, maternal lymphocytes were identified by in situ hybridization (XX
chromosomes) and immunohistochemistry (CD3) in the placental villi of male fetuses [26],
and in some fetal tissues during autopsy (liver, spleen, thymus) [27]. Similarly, CD4 and
CD8 lymphocytes of maternal origin were found in the serum of nine boys with apparently
idiopathic inflammatory myopathy [28] and the maternal allele HLA-DQA1 was spotted in
circulation of 15 boys struck by dermatomyositis [29].

Contributing factors were the CVUE analysed by Becroft et al. [3]: after adjusting for the
community affected by IUGR, there is the negative role of maternal body mass index (BMI)
higher (p = 0.04), the multiple pregnancy (p = 0.03), urinary complications during
pregnancy (p = 0.05) and ethnicity (p = 0.03), with a lower prevalence among Maori,
Chinese and Hindus.

The consequences of chronic villitis of unknown etiology

INTERUTERINE GROWTH RESTRICTION/RETARDATION (IUGR)
About 63 term placentas, 44 were for IUGR, Labarrere et al. [19] showed that, in normal
children, there were 1.2% of the villi in an inflammatory reaction against 10% in cases of
IUGR. Then the same team observed that this villite was more frequent in the IUGR was
more severe [20]. Twenty-five to thirty percent of IUGR considered idiopathic actually are
associated with lesions of chronic villite [30, 31]. Similarly, the CVUE is twice as common
when fetal growth was slower than when it was normal (OR = 2.35, 95% CI: 1.55 to 3.56)

[3]. Before 32, Salafia et al. [32] found themselves a CVUE in 3.2% of normal weight children, against 6.3% of symmetrical IUGR and 12% of asymmetric IUGR (p <0.001). This chronic inflammation is most often found in apparently idiopathic IUGR in cases of gestational hypertension, where the predominant lesions in the vessels on the maternal side [33, 34]. In twin pregnancies, the discrepancy in weight between the twins can be explained partly by a higher frequency of lesions in twin CVUE reached [35, 36]. The origin of IUGR is to seek, first, in association with the histological CVUE endovascularite of colitis [31, 37], on the other hand, in the role of cytokines that may inhibit phosphoenolpyruvate carboxykinase involved in gluconeogenesis [1, 3].

PREMATURE BIRTH
The activation mechanism of inflammation of the CVUE was also frequently described in the placentas of preterm delivery: 4% between 22 and 28 weeks, 9% between 29 and 32 weeks, 16% between 33 and 36 weeks. CVUE are more frequent in the spontaneous preterm births without infectious context when there are signs of bacterial infection normally visible as a vascularity of the umbilical cord (17% vs 8%, p <0, 05) [38].

AUTOIMMUNE DISEASES
Given the implications of immunological certain pathologies, it is not surprising to find, in addition to uterine vascular lesions and thrombosis, more CVUE if disseminated lupus erythematosusmatous (28% versus 5.5%) [39] and especially in antiphospholipid syndrome (APS), mainly during late miscarriages after 18 weeks, and more often during the APS symptomatic questions in abortions that occurred after only serological APS (p = 0.07) [40, 41] .

PRE-ECLAMAPSIA
The CVUE is expressed mostly in the placental lots of very preterm births, 22 to 32 weeks, in a context of pre-eclampsia than in preterm deliv-chements spontaneous or occurring after premature rupture of membranes (20% vs 3%, p <0.001) [42]. Labarrere Althabe and [43] have found CVUE in 25% of placentas after normal pregnancy, 26% of products delivers after chronic arterial hypertension (HTAC) and 80% of the organs examined after pre-eclampsia superimposed on a HTAC.

PERIPARTUM ASPHYXIA
Finally, the CVUE is part of placental lesions which weaken the fetus at birth, that can Salafia et al. [44] showed a decrease in pH (p <0.05) and PO2 (p <0.001) and increased PCO2 (p <0.05) in the umbilical artery during deliveries very preterm with this type of lesions. CVUE also has medico-legal implications since it allows to relate to neonatal seizures and neurological disabilities associated to this pathology have been linked to antenatal peripartum asphyxia [45-47]. The CVUE was also highlighted in the context of severe neonatal thrombocytopenia in relation to allo-immunization anti-HPA [48] or anti-HLA class I [49]. In the latter case, it appears that brain damage can result from not only bleeding but also because of thrombosis of class I antibodies can damage endothelial cells via cytokines by promoting platelet aggregation and releasing tissue factor in the extrinsic pathway of coagulation [50-53]. In our observation CIUE, where anti-HLA antibodies were demonstrated in class I and II, severe thrombocytopenia had been demonstrated in children, even when it is the second birth.

Chronic intervillositis of unknown etiology

The second placental pathology where there is a chronic inflammatory response is chronic intervillosistis which effects the intervillous chambers. The boundaries with chronic villitis have not been clearly defined because there are associations between the two pathologies. It is perfectly possible to deduce that initially the immune reaction moves into the intervillous space, then diffusing into the fetal circulation.

In certain circumstances, the chronic intervillosistis is easily linked to the symptoms of antiphospholipid syndrome [41], and malaria infection with massive presence of pigment deposits of parasites or parasitised erythrocytes [54, 55].

In the absence of well-defined cause, it is Chronic intervillositis of unknown etiology (CIUE) [8]. The literature identifies only four publications specifically addressing CIUE, contrasting with the abundance of literature on chronic villitis.

Doss et al. [56] described the massive CIUE in a patient that had suffered 10 spontaneous miscarriages.
In fact, looking for CIUE lesions is quite interesting, in cases of miscarriage. While aspects of hydropic villi and dysmorgraphic evokes chromosomal abnormalities rather than with a positive predictive value (PPV) of 90% before 6 weeks, aspects of CIUE have a PPV of 85% for a normal karyotype in abortions after the 11.5 weeks [57, 58]. In the series of Boyd and Redline [59], the frequency of lesions CIUE went from 22/1000 on a first miscarriage with a normal karyotype to 80/1000 in cases of recurrence.

Labarrere and Mullen [8] reported 6 cases with 5 IUGR and a perinatal death. In the statistics of 6 cases of Jacques and Qureshi [60], the lesions were associated with placental of fibrinoid deposits (6 cases), infarction (2 cases), aspects of atheroma in decidual vessels (2 cases) and of acute chorioamnionitis in 2 cases. The largest series is that of Boyd and Redline [59] reported exclusively on 31 sufferers of CIUE, no other villous extensions, with confirmation by immunohistochemistry of a conflict of immunological origin. The prognosis of these pregnancies was very unfavorable, with 77% of perinatal deaths, 57% of IUGR and only 18% of pregnancies reaching 37 weeks. It is, however, a rare disease because it was only found in 0.6 / 1000 placentas collected during the second and third trimesters.

Recently, in two cases of intrauterine fetal death (IUFD), Out et al. [61] found, in one case, a CVUE and in the other, a CIUE.

An unpublished work of Parant et al. [62] performed in Toulouse, involved 13 pregnancies in 9 patients with lesions typical of CIUE. The disease incidence was estimated at 0.9 / 1,000 births. In this series, there was no ethnic predisposition, or problems of immunological, thrombophilic nature nor abnormality of serum markers in second trimester of pregnancy. Perinatal mortality was 56%, with only 15% of pregnancies beyond 37 weeks and a very high percentage of delayed intrauterine growth retardation (IUGR): in this case 82% in pregnancies beyond 22 weeks, and 60% children born alive.

Recurrences Chronic intervillositis of unknown etiology
Reviewing the history of their patients, Parant et al. [62] that quoted that 2 of 9 women

had a history of recurrent miscarriage, some women had a normal pregnancy prior to the first incident CIUE, but thereafter placental lesions systematically recurred. Our observation shows CIUE incidents ever earlier. Overall, the series of Boyd and Redline [59], the rate of recurrences of CIUE was 67%. It is thus noted that, unlike pre-eclampsia, where the antibodies blocking the rejection of fetal allograft function appear to increase with each pregnancy with the same partner in the case of chronic villitis and intervillositis of immune origin, incidents are repeated and apparently occur more severely and earlier.

<u>The Possible Therapies</u>

It should be remembered that the diagnosis of chronic inflammatory lesions can only be made after a histological examination of the placenta. This should be asked for when faced with any IUGR and premature delivery of unknown cause, in case of preeclampsia and perinatal asphyxia or unexplained death in utero. Boyd and Redline [59] reported two successes with the use of progesterone. Given the vascular occlusive lesions associated with lymphocytes and plasma cells infiltrate, we think it is logical to treat these patients with aspirin after 12 weeks. However, as shown by our second observation, this treatment is not enough. The immunological reaction must also be fought with corticosteroids. Parant et al. [62] reported three pregnancies in their series treated with aspirin and Prednisone: outcomes of these pregnancies were: an early miscarriage, fetal death in utero at 37 weeks and only one live birth after a cesarean 34 weeks (child's weight: 2410g). In our first case of chronic villitis, the choice of corticosteroid was decided on based on the good cross placenta transmission by betamethasone (2 mg/day). One can observe that this treatment resulted in a live birth, but it has not eliminated the inflammatory lesions of the placenta, either because of an inadequate steroid, either because of an insufficient dosage. However, in the second observation villitis and intervillositis chronic dose of 20 mg of prednisone started at the 23rd week has been correlated to a total absence of chronic inflammatory lesions during the examination of the placenta. This choice of prednisone appeared to us more logical if one assumes that the inflammatory response seen in the intervillous space is probably of maternal origin. Most recently, Althaus et al. [48] found that treatment of allo-immunization by anti-platelet immunoglobulins (IVIG) reduced the rate of CVUE from 83 to 0%.

CONCLUSION

The villitis and intervillositis of undetermined origin are histological lesions of the placenta still unclear. During pregnancy, chronic villitis was associated with elevated levels of alpha-feto-protein in the context of IUGR [63] or non-significant elevations of hCG [64] when testing bio- logical screening of trisomy in the second quarter. They must be sought routinely when a placenta from a pathological pregnancy is addressed to a department of pathology, especially in the context of miscarriage, prematurity and IUGR, unexplained acute fetal suffering because of non-obvious and IUFD [65]. There is no urgency to dispose of a placenta during an apparently normal pregnancy. As suggested by Badawi et al. [66], it would be judicious to keep the all placentas refrigerated for 72 hours, until satisfied that the child showed no abnormal neurological symptoms, he did not been transferred to neonatal intensive care and there has not died quickly. The origin of chronic inflammatory

disease of the placenta is probably immune by fetal allograft rejection, related to the lack of production of blocking antibodies. Due to the recurrence of lesions, preventative therapy with aspirin and corticosteroids should be considered.

RÉFÉRENCES

1. Altshuler G, Hyde SR. Clinicopathologic implications of placental pathology. *Clin Obstet Gynecol* 1996; *39* : 549-70.

2. Nessmann C, Larroche JC. Villite et intervillite chroniques sans étiologie connue. *In* : Atlas de pathologie placentaire. Masson, Paris, 2001, p. 67-68.

3. Becroft DM, Thompson JM, Mitchell EA. Placental villitis of unknown origin : epidemiologic associations. *Am J Obstet Gynecol* 2005; *192* : 264-71.

4. Knox WF, Fox H. Villitis of unknown aetiology: its incidence and significance in placentae from a British population. *Placenta* 1984; *5*: 395-402.

5. Russell P. Inflammatory lesions of the human placenta. III. The histopathology of villitis of unknown aetiology. *Placenta* 1980; *1* : 227-44.

6. Altshuler G, Russell P, Ermocilla R. The placental pathology of small-for-gestional age infants. *Am J Obstet Gynecol* 1975 ; *121* : 351-9.

7. Russell P. Inflammatory lesions of the human placenta. II. Villitis of unknown etiology in perspective. *Am J Diagn Gynecol Obstet* 1979 ; *1* : 351-9.

8. Labarrere C, Mullen E. Fibrinoid and trophoblastic necrosis with massive intervillitis: an extreme variant of villitis unknown etiology. *Am J Reprod Immunol Microbiol* 1987 ; *15* : 85-91.

9. Benirschke K, Coen R, Patterson B, Key T. Villitis of known origin : varicella and toxoplasma. *Placenta* 1999 ; *20* : 395-9.

10. Qureshi F, Jacques SM. Maternal varicella during pregnancy: correlation of maternal history and fetal outcome with placen- tal histopathology. *Hum Pathol* 1996 ; *27* : 191-5.

11. Genest DR, Choi-Hong SR, Tate JE, Qureshi F, Jacques SM, Crum C. Diagnosis of congenital syphilis from placental examination : comparison of histopathology, Steiner stain, and polymerase chain reaction for Treponema pallidum DNA. *Hum Pathol* 1996 ; *27* : 366-72.

12. Qureshi F, Jacques SM, Reyes MP. Placental histopathology in syphilis. *Hum Pathol* 1993 ; *24* : 779-84.

13. Nakamura Y, Sakuma S, Ohta Y, Kawano K, Hashimoto T. Detection of the human cytomegalovirus gene in placental vilitis by polymerase chain reaction. *Hum Pathol* 1994 ; *25* : 815-8.

14. Abramowsky C, Beyer-Patterson P, Cortinas E. Nonsyphilitic spirochetosis in second-trimester fetuses. *Pediatr Pathol* 1991 ; *11* : 827-38.

15. Jacques SM, Qureshi F. Chronic chorioamnionitis: a clinicopathologic and immunohistochemical study. *Hum Pathol* 1998 ; *29* : 1457-61.

16. Gersell DJ. Chronic villitis, chronic chorioamnionitis, and maternal floor infarction. *Semin Diagn Pathol* 1993 ; *10* : 251-66.

17. Redline RW, Ariel I, Baergen RN, Desa DJ, Kraus FT, Roberts DJ *et al.* Fetal vascular obstructive lesions : nosology and repro- ducibility of placental reaction patterns. *Pediatr Dev Pathol* 2004 ; *7* : 443-52.

18. Khong TY, Staples A, Moore L, Byard RW. Observer reliability in assessing villitis of unknown aetiology. *J Clin Pathol* 1993 ; *46* : 208-10.

19. Labarrere C, Althabe O, Telenta M. Chronic villitis of unknown aetiology in placentae of idiopathic small for gestational infants. *Placenta* 1982 ; *3* : 309-17.

20. Althabe O, Labarrere C. Chronic villitis of unknown aetiology and intrauterine growth-retarded infants of normal and low ponderal index. *Placenta* 1985 ; *6* : 369-73.

21. Labarrere C, Althabe O, Caletti E, Muscolo D. Deficiency of blocking factors in intrauterine growth retardation and its rela- tionship with chronic villitis. *Am J Reprod Immunol Microbiol* 1986 ; *10* : 14-9.

22. Labarrere C, Althabe O. Intrauterine growth retardation of unknown etiology: II. Serum complement and circulating immune complexes in maternal sera and their relationship with parity and chronic villitis. *Am J Reprod Immunol Microbiol* 1986 ; *12* : 4-6.

23. Labarrere C, Faulk WP, McIntyre JA. Villitis in normal term human placentae: frequency of the lesion determined by monoclonal antibody to HLA-DR antigen. *J Reprod Immunol* 1989 ; *16* : 127-35.

24. Labarrere C, McIntyre JA, Faulk WP. Immunohistologic evidence that villitis in human normal term placentas is an immunologic lesion. *Am J Obstet Gynecol* 1990 ; *162* : 515-22.

25. Labarrere C, Carson SD, Faulk WP. Tissue factor in chronic villitis of unestablished etiology. *J Reprod Immunol* 1991 ; *19* : 225-35.

26. Redline RW, Patterson P. Villitis of unknown etiology is associated with major infiltration of fetal tissue by maternal inflammatory cells. *Am J Pathol* 1993 ; *143* : 473-9.

27. Götherström C, Johnsson AM, Mattsson J, Papadogiannakis N, Westgren M. Identification of maternal hematopoietic cells in a 2nd-trimester fetus. *Fetal Diagn Ther* 2005 ; *20* : 355-8.

28. Artlett CDM, Ramos R, Jiminez SA, Patterson K, Miller FW, Rider LG, for the Childhood Myositis Heterogeneity Collaborative Group. Chimeric cells of maternal origin in juvenile idio- pathic inflammatory myopathies. *Lancet* 2000 ; *356* : 2155-6.

29. Reed AM, Picornell YJ, Harwood A, Kredich DW. Chimerism in children with juvenile dermatomyositis. *Lancet* 2000 ; *356* : 2156-7. 30. Altshuler G, Russell P, Ermocilla R. The placental pathology of the small-for-gestational age infants. *Am J Obstet Gynecol* 175 ; *121* : 351-9.

31. Salafia CM, Vintzileos AM, Silberman L, Bantham KF, Vogel CA. Placental pathology of idiopathic intrauterine growth retarda- tion at term. *Am J Perinatol* 1992 ; *9* : 179-84.

32. Salafia CM, Minior VK, Pezzullo JC, Popek EJ, Rosenkrantz TS, Vintzileos AM. Intrauterine growth restriction in infants of less than thirty two weeks' gestation : associated placental patho- logic features. *Am J Obstet Gynecol* 1995 ; *173* : 1049-57.

33. Redline RW, Patterson P. Patterns of placental injury. Correlations with gestational age, placental weight, and clinical diagnoses. *Arch Pathol Lab Med* 1994 ; *118* : 698-701.

34. Salafia CM, Ernst LM, Pezzulllo JC, Rosenkrantz TS, Vintzileos AM. The very low birth weight infant : maternal complications leading to preterm birth, placental lesions, and intrauterine growth. *Am J Perinatol* 1995 ; *12* : 106-10.

35. Jacques SM, Qureshi F. Chronic villitis of unknown etiology in twin gestations. *Pediatr Pathol* 1994 ; *14* : 575-84.

36. Eberle AM, Levesque D, Vintzileos AM, Egan JF, Tsapanos V, Salafia CM. Placental pathology in discordant twins. *Am J Obstet Gynecol* 1993 ; *169* : 931-5.

37. Sander CM, Gilliland D, Flynn MA, Swart-Hills LA. Risk factors for recurrence of hemorrhagic endovascularitis of the placenta. *Obstet Gynecol* 1997 ; *89* : 569-76.

38. Salafia CM, Vogel CA, Vintzileos AM, Bantham KF, Pezzullo J, Silberman L. Placental pathologic findings in preterm birth. *Am J Obstet Gynecol* 1991 ; *165* : 934-8.

39. Magid MS, Kaplan C, Sammaritano LR, Peterson M, Druzin ML, Lockshin MD. Placental pathology in systemic lupus erythematosus : a prospective study. *Am J Obstet Gynecol* 1998 ; *179* : 226-34.

40. Salafia CM, Parke A. Placental pathology in the phospholipid antibody syndrome and systemic lupus erythematosus. *Am J Obstet Gynecol* 1995 ; *172* : 336 (Abstr. 273).

41. Salafia CM, Cowchok FS. Placental pathology and antiphospholipid antibodies : a descriptive study. *Am J Perinatol* 1997 ; *14* : 435-41.

42. Salafia CM, Pezzullo JC, Lopes-Zeno JA, Simmens S, Minior VK, Vintzileos AM. Placental pathologic features of preterm pree- clampsia. *Am J Obstet Gynecol* 1995 ; *173* : 1097-105.

43. Labarrere C, Althabe O. Chronic villitis of unknown aetiology and decidual maternal vasculopathies in sustained chronic hypertension. *Eur J Obstet Gynecol Reprod Biol* 1986 ; *21* : 27-32.

44. Salafia CM, Minior VK, Lopez-Zeno JA, Whittington SS, Pezzullo JC, Vintzileos AM. Relationship between placental histologic features and umbilical cord blood gases in preterm gestations. *Am J Obstet Gynecol* 1995 ; *173* : 1058-64.
45. Redline RW, O'Riordan MA. Placental lesions associated with cerebral palsy and neurologic impairement following term birth. *Arch Pathol Lab Med* 2000 ; *124* : 1785-91.

46. Scher MS, Trucco GS, Beggardly ME, Steppe DA, Macpher- son TA. Neonates with electrically confirmed seizures and possible placental associations. *Pediatr Neurol* 1998 ; *19* : 37- 41.

47. Redline RW. Severe fetal placental vascular lesions in term infants with neurologic impairement. *Am J Obstet Gynecol* 2005 ; *192* : 452-7.

48. Althaus J, Weir EG, Askin F, Kickler TS, Blakemore K. Chronic villitis in untreated neonatal alloimmune thrombocytopenia : an etiology for severe early intrauterine growth restriction and the effect of intravenous immunoglobulin therapy. *Am J Obstet Gynecol* 2005 ; *193* : 1100-4.

49. De Tar MW, Klohe E, Grosset A, Rau T. Neonatal alloimmune thrombocytopenia with HLA alloimmunization: case report with immunohematologic and placenta findings. *Pediatr Dev Pathol* 2002 ; *5* : 200-5.

50. Brandt JT, Julius CJ, Osborne JM, Anderson CL. The mecha- nism of platelet aggregation induced by HLA-related antibo- dies. *Thromb Haemost* 1996 ; *76* : 774-9.

51. Labarrere CA, Esmon CT, Carson SD, Faulk WP. Concordant expression of tissue factor and class II MHC antigens in human placental endothelium. *Placenta* 1990 ; *11* : 309-18.

52. Labarrere CA, Carson SD, Faulk WP. Tissue factor in chronic villitis of unestablished etiology. *J Reprod Immunol* 1991 ; *19* : 225-35.

53. Faulk WP, Labarrere CA, Carson SD. Tissue factor : identifi- cation and characterization of cell types in human placenta. *Blood* 1990 ; *76* : 86-96.

54. Ordi J, Ismail MR, Ventura PJ, Kahigwa E, Hiret R, Cardesa A *et al.* Massive chronic intervillositis of the placenta associated with malaria infection. *Am J Surg Pathol* 1998 ; *22* : 1006-11.

55. Nebuloni M, Pallotti F, Polizzotti G, Pellegrinelli A, Tosi D, Giordano F. Malaria placental infection with massive chronic intervillositis in a gravida 4 woman. *Hum Pathol* 2001 ; *32* : 1022-1023.

56. Doss BJ, Greene MF, Hill J, Heffner LJ, Bieber FR, Genest DR. Massive chronic intervillositis associated with recurrent abortions. *Hum Pathol* 1995 ; *26* : 1245-51.

57. Redline RW, Zaragoza M, Hassold T. Prevalence of develop-
mental and inflammatory lesions in nonmolar first-trimester spontaneous abortions. *Hum Pathol* 1999 ; *30* : 93-100.

58. Salafia C, Maier D, Vogel C, Pezzullo J, Burns J, Silberman L.
Placental and decidual histology in spontaneous abortion : detailed description and correlations with chromosome num-
ber. *Obstet Gynecol* 1993 ; *82* : 295-303.

59. Boyd TK, Redline RW. Chronic histiocytic intervillositis: a pla-
cental lesion associated with recurrent reproductive loss. *Hum Pathol* 2000 ; *31* : 1389-96.

60. Jacques SM, Qureshi F. Chronic intervillositis of the placenta.
Arch Pathol Lab Med 1993 ; *117* : 1032-5.

61. Hors Y, Jacob B, Brousse H, Beniada A, Herlicoviez M,
Dreyfus M. Villites et intervillites chroniques placentaires : une cause de mort fœtale *in utero* inexpliquée. *J Gynecol Obstet Biol Reprod* 2000 ; *29* : 712.

62. Parant O, Capdet J, Aziza J, Kessler S, Céré N, Berrebi A.
Intervillite chronique sans étiologie connue. XXXIVe Journées de la Société Française de Médecine Périnatale, Dijon, 27-
29 octobre 2004 (Abstract)

63. Salafia CM, Silberman L, Herrera NE, Mahoney MJ. Placental
pathology at term associated with elevated midtrimester serum alpha-fetoprotein concentration. *Am J Obstet Gynecol* 1988 ; *158* : 1064-6.

64. Lin DFR, Dickerman LH, Redline RW. Pathologic findings in
pregnancies with unexplained increases in midtrimester maternal serum human chorionic gonadotropin levels. *Am J Clin Pathol* 1999 ; *111* : 209-15.

65. Agapitos E, Papadopoulou C, Kavantzas N, Papoulias J,
Antonaki V, Davaris P. The contribution of pathological exa- mination of the placenta in the investigation of the causes of foetal mortality. *Arch Anat Cytol Pathol* 1996 ; *44* : 5-11.

66. Badawi N, Kurinczuk JJ, Keogh JM, Chambers HM, Stanley FJ.
Why is the placenta being ignored? *Aust N Z J Obstet Gynae- col* 2000 ; *40* : 343-6.