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Chronic histiocytic intervillositis of unknown etiology: Clinical features in a consecutive series of 69 cases

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ABSTRACT

Introduction: Chronic histiocytic intervillositis of unknown etiology (CIUE) is a rare placental inflammatory disease, associated with severe obstetric complications. Its pathophysiologic mechanism remains to be elucidated.
Aim: To establish anatomical–clinical correlations to improve our understanding of CIUE pathophysiology.
Material and methods: Retrospective study of all cases of CIUE occurring during a 9-year period in a university tertiary hospital center.
Results: CIUE was diagnosed in 69 pregnancies in 50 different women, after early spontaneous abortions (30.4%), late spontaneous abortions (13.0%), *in utero* deaths (26.1%), and live births (30.4%). Of 39 fetuses surviving to at least 22 weeks, 24 had severe intrauterine growth restriction (61.5%) and 18 died *in utero* (46.2%). Twelve *in utero* deaths occurred before 32 weeks of gestation (66.7%). Substantially elevated alkaline phosphatase levels (>600 IU/L) were observed in 55.6% of cases. Microscopic examination of placentas showed that both spontaneous early abortions and intrauterine growth restriction were significantly associated with more intense fibrin deposits.
Conclusion: A diagnosis of CIUE must be considered in cases of severe obstetric complications. We hypothesize that the elevated alkaline phosphatases (ALP) observed during the pregnancy demonstrate the presence of syncytiotrophoblastic lesions due to histiocytosis in the intervillous space, before fibrin deposits cover them.

1. Introduction

First described in the literature by Labarrere and Mullen in 1987 [1], chronic intervillositis of unknown etiology (CIUE) is an inflammatory placental disease defined by its microscopic appearance. It is also known as nonspecific chronic histiocytic intervillositis and massive chronic intervillositis [1–3].

Chronic histiocytic intervillositis lesions are located in the intervillous space and are characterized by extensive infiltration of inflammatory cells, mainly mononuclear cells of maternal origin (histiocytes) [4,5], together with fibrin deposits and trophoblastic erosion of varying degrees [1,3]. These lesions may be diffuse (massive infiltration) or multifocal, sometimes predominantly on the maternal side of the placenta. This disease is considered nonspecific (CIUE) when accompanied by no signs of either villitis or other placental lesions [2].

CIUE is a rare disease (9.6 per 1000 spontaneous abortions and 0.6 per 1000 placentas examined in the second and third trimesters) [2]. It is a cause of concern because of the severe obstetric complications linked to it: early and late spontaneous abortions, intrauterine growth restriction (IUGR), *in utero* deaths, all with a risk of recurrence that has not been adequately assessed but which seems real [2,3,6,7]. The mechanism linking these associations is not completely known. The hypothesis of an immune conflict has been mentioned but remains to be demonstrated [1,2,7–9].

To understand this rare and poorly understood entity better, we have conducted a retrospective study with clinicoanatomic comparisons intended to clarify the characteristics of pregnancies complicated by CIUE and to establish a relation between the pathologic characteristics of the intervillositis and the severity of the obstetric situation.

2. Material and methods

This retrospective study reviewed all cases of CIUE diagnosed at our university hospital center from 1997 through 2006. For placental analysis, products of conception were fixed in formalin within 24 h (for first-trimester abortions) and

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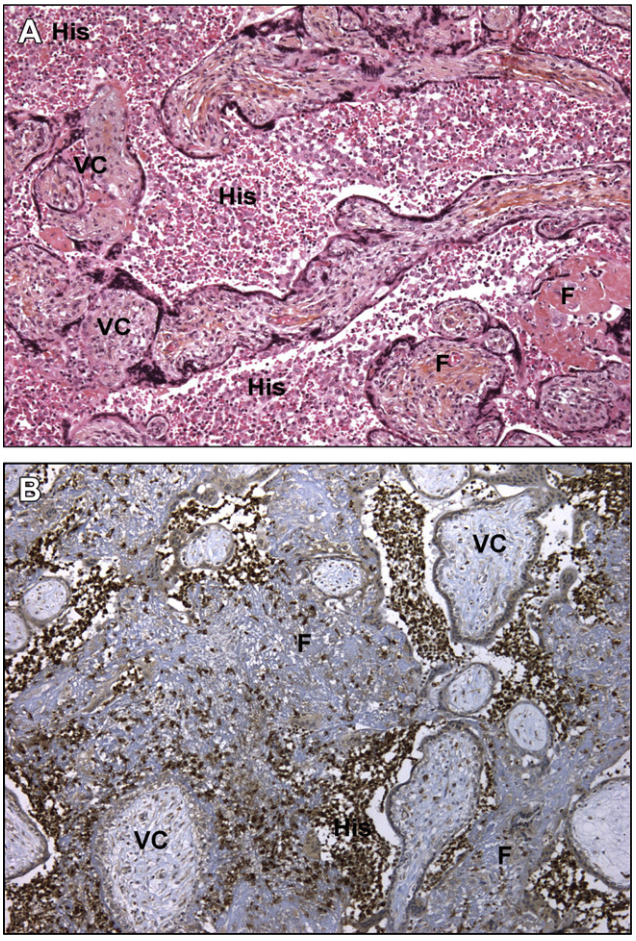

Fig. 1. Normal placenta (A) and histiocytic intervillositis (B and C) in the third trimester of pregnancy. (CV = Chronic villi, F = Fibrin, H = Histiocytes) Histiocytic intervillositis (HES staining, magnification ×400). The intervillous space is completely filled by maternal mononuclear cells. B. Histiocytic intervillositis (magnification ×400, immunohistochemistry). Staining by anti-CD 68 antibodies shows that the mononuclear cells that have invaded the intervillous space are histiocytes.

placentas within one week. Multiple samples were then set in paraffin blocks 3 μm thick for HES (hematoxylin-eosin-saffron) staining. Each slide was reread by two pathologists specialized in fetal pathology (LD and SP). The diagnosis of intervillositis was based on the presence in the intervillous space of mononuclear cellular infiltrate, predominantly histiocytic, whether or not accompanied by fibrin deposits (Fig. 1). The histiocytic origin of the infiltrate was systematically confirmed by testing for anti-CD 68 antibodies (mouse monoclonal antibodies, clone PGM1 DakoCytomation ®, dilution 1/1000, EDTA pretreatment buffer, incubation, DAB revelation, Glostrup, Denmark). Cases with intervillites associated with other placental lesions were excluded from the study.

The intervillositis was considered diffuse when there were clusters of histiocytes filling the entire intervillous space uniformly and massively at a magnification ×100 and was multifocal when the clusters were distributed heterogeneously in the intervillous spaces, varying from one microscopic field to another. The intensity of intervillositis was considered high when the clusters of histiocytes completely filled the intervillous space, moderate when the clusters were less voluminous, and low when they contained only a few histiocytes. The intensity of the fibrin deposits was considered high when they filled the intervillous spaces over several fields, moderate when these deposits were inconsistent, and low when there were only several scattered deposits.

Maternal and obstetric data were collected from each patient's obstetric records. All patients who reached the sixth month of pregnancy had an O'Sulllivan test, routinely performed to screen for pregnancy-related diabetes. When they were available, other laboratory results were noted: alkaline phosphatases (ALP), transaminases, antinuclear antibodies, anticardiolipin antibodies, antiprothrombinase antibodies, C-reactive protein, placental cultures, counts of red blood cells, leukocytes, and platelets, and workups for constitutional thrombophilia. The ALP level was defined as abnormal when it exceeded 600 IU/L, that is, 2.5 times the normal level outside pregnancy. In three cases, we sought to determine if the PAL isoenzymes derived from the placenta by agarose gel electrophoresis before and after heating the sample to 65 °C (Hydragel 7 ISO-PAL Kit, Hydrasys, SEBIA, Evry, France). Preeclampsia was diagnosed when blood pressure ≥140/90 mm Hg and proteinuria >300 mg/L or ≥2+ on the urinary dipstick. Finally, weight, gestational age, and vital status of the fetus were recorded. IUGR was defined by a weight below the third percentile on the Leroy–Lefort curves used in France [10].

The data were recorded and analyzed with Epi Info software (Version 6.04, Atlanta, GA, USA). Comparisons between qualitative data used the Chi-square test or Fisher's exact test, when the number of individuals was low. Comparisons between quantitative variables used Wilcoxon's nonparametric test. All tests were bilateral and the significance level was set at $p < 0.05$. The tables report percentages between parentheses, means with the standard deviations of their distributions, and ranges between square brackets.

Table 1
Characteristics of 69 pregnancies with CIUE (among 50 patients).

Patient characteristics	
Pregnancy outcome	
Early spontaneous abortion ≤12 weeks)	21 (30.4)
Late spontaneous abortion (13–22 weeks)	9 (13.0)
Birth ≥22 weeks	39 (56.5)
Age	31.2 ± 6.1 [16–43]
Mother smoked	12 (17.4)
Autoimmune disease[a]	3/50 (6.0)
No previous pregnancy	7 (10.1)
No previous liveborn children	9 (13.0)
Pregnancies ≥22 weeks (n = 39)	
Sex ratio M/F	1.17
Preeclampsia	3/39 (7.7)
IUGR ≤ 3rd percentile	24/39 (61.5)
In utero deaths	18/39 (46.2)
Abnormal umbilical Doppler[b,c]	11/35 (31.4)
Abnormal uterine Doppler[b,d]	14/35 (40.0)
Elevated ALP (≥2.5 N)[e]	10/18 (55.6)

[a] Autoimmunes diseases: among 50 patients, one patient had an isolated Hashimoto thyroid, one had an thyroiditis from unspecified causes, and the last one had an Hashimoto thyroid associated with mixed connective tissue disease, thrombocytopenia purpura and systemic lupus erythematosus.
[b] Information about umbilical and uterine artery Doppler findings was not available for 4 pregnancies.
[c] The umbilical artery Doppler was considered abnormal if the resistance index was abnormal for the gestational age considered or in cases of absent diastole and/or reverse flow.
[d] If the resistance index was elevated ($N > 0.60$) and/or a uni or bilateral notch was present.
[e] The alkaline phosphatase assay was performed in 18 cases. In three cases, a placental cause for the ALP was sought and confirmed.

3. Results

This study analyzed the results for products of conception from 2616 early abortions (before 12 weeks of gestation) as well as 6370 placentas (after 12 weeks of gestation) that were examined during the study period. In all, 69 cases met the criteria defining CIUE; they involved 50 patients who had a total of 224 pregnancies (CIUE thus affected 30.8% of their pregnancies).

Slides and pathology reports were reviewed for these 69 pregnancies (Table 1): 21 early spontaneous abortions ≤12 weeks (30.4%), 9 late spontaneous abortions from 12 to 22 weeks (13.0%), and 39 births after 22 weeks, whether live- or still-born (56.5%).Regardless of the period of pregnancy considered, CIUE accounted for 0.8% of the products of conception examined in our laboratory (before 12 weeks: 21/2616, that is, 0.8%–95%CI [0.5–1.2]; from 12 to 22 weeks: 48/6370: 0.8%–95%CI [0.6–1.0]).

Twelve of the 50 (24.0%) women had at least three spontaneous abortions ≤22 weeks, half of them consecutively (12.0%). Three patients had a preexisting autoimmune disease (6.0%). Two women (4.0%) had abnormalities identified by the thrombophilia workup: one a heterozygous factor V Leiden mutation and the other an

Table 2
Comparison of pregnancies that lasted more than 22 weeks, according to their outcome.

	In utero death $n = 18$	Liveborn child $n = 21$	p
Gestational age at outcome (weeks)	30.5 ± 5.6 [22.0–40.4]	35.0 ± 2.5 [30.6–39.0]	<0.05
≤32 weeks:	12 (66.7)	4 (19.0)	<0.01
32–37 weeks:	4 (22.2)	9 (42.9)	
≥37 weeks	2 (11.1)	8 (38.1)	
Birth weight (g)	1300 ± 1200 [80-3610]	1780 ± 590 [920-2830]	<0.05
IUGR ≤ 3rd percentile	11 (61.1)	13 (62.0)	NS
Gestational age *at diagnosis*	22.2 ± 6.4	27.3 ± 4.5	<0.05
Gestational age *at birth*	28.0 ± 4.4	34.2 ± 2.7	<0.05
Abnormal umbilical artery Doppler	2/11 (18.2)	9/13 (69.2)	NS
Abnormal uterine artery Doppler	5/11 (45.5)	9/13 (69.2)	NS
Elevated ALP (≥2.5 N)[a]	4/10 (40.0)	6/8 (75.0)	NS
[2.5N–5N]	1	1	NS
[5N–10N]	1	5	
>10 N	2	0	

[a] All the pregnancies in which alkaline phosphatases were elevated had an IUGR below the 3rd percentile. In three cases, a placental cause for the ALP was sought and confirmed.

isolated reduction of coagulation factors II and V. The 8 parental and 16 fetal karyotypes performed were all normal. Of these 69 pregnancies, only 9 concerned nulliparas (13.0%) and 12 women who smoked during pregnancy (17.4%). Of the pregnancies that reached 22 weeks, only three involved preeclampsia (7.7%), but almost two thirds were marked by severe IUGR, often with abnormal Doppler spectra for the uterine and umbilical arteries. Overall the outcome for almost half the pregnancies with CIUE (46.2%) was *in utero* death. Finally, alkaline phosphatase assays were performed for 18 pregnancies (26.1%). They showed ALP levels greater than 2.5 times normal in more than the half the cases.

Three quarters of the children were born preterm (29/39, that is, 74.4%) (Table 2). Although three quarters of the *in utero* deaths occurred before 32 weeks of gestation (66.7%), only 19% of the liveborn children were born before that term ($p < 0.01$). There were as many children with severe IUGR among those who died *in utero* as among those liveborn. On the other hand, gestational age at IUGR diagnosis was earlier for the children who died *in utero* (22.2 vs 27.3 weeks, $p < 0.05$), with death around 28.0 weeks, while the liveborn children were born later, at an average of 34.2 weeks ($p < 0.05$). Of the pregnancies with very high ALP levels, 80.0% had severe IUGR (data not shown). Two *in utero* deaths occurred in mothers with ALP levels more than 10 times normal, but there was no significant difference in ALP levels according to whether the fetus did or did not die *in utero*.

Table 3
Characteristics of pregnancies in patients with at least one known recurrence of CIUE.

	Recurrence $n = 28$	Single episode $n = 41$	p
Number of patients	9	41	
Number of pregnancies with CIUE per patient	3.1 ± 1.5	1.0	
Spontaneous abortions	16 (57.1)	14 (34.1)	0.06
Early (≤12 weeks)	12	9	
Late (13–22 weeks)	4	5	
Pregnancies ≥ 22 weeks	$n = 12$	$n = 27$	
Birth weight	1570 ± 900	1570 ± 950	NS
GA (weeks):	31.8 ± 4.7	33.4 ± 4.8	NS
IUGR ≤ 3rd percentile	7 (58.3)	17 (63.0)	NS
In utero death	7 (58.3)	11 (40.7)	NS
In utero deaths	$n = 7$	$n = 11$	
IUGR ≤ 3rd percentile	5 (71.4)	6 (54.5)	NS
GA (weeks) at birth	29.5 ± 4.7	31.2 ± 6.2	NS
Birth weight	1070 ± 930	1400 ± 1340	NS
Liveborn children	$n = 5$	$n = 16$	
IUGR ≤ 3rd percentile	2 (40.0)	11 (68.8)	NS
GA (weeks) at birth	35.0 ± 2.0	34.9 ± 2.7	NS
Birth weight	2060 ± 580	1690 ± 580	NS

Nine of the 50 women had at least one documented recurrence of CIUE (18%). These nine women had 59 pregnancies, 28 with CIUE (3.1 CIUE pregnancies per patient) (Table 3). Compared with the 41 patients who apparently had only a single episode of CIUE, these nine women tended to have a higher frequency of spontaneous abortions (57.1 vs 34.1, $p = 0.06$). Moreover, seven of them had at least three spontaneous abortions ≤ 22 weeks (77.8%), consecutively for four of them (57.1%). These two groups (with recurrence vs. single-episode) did not differ significantly in any important aspect for pregnancies that lasted at least 22 weeks. Specifically, they did not differ for gestational age, birth weight, percentage of infants with severe IUGR or of *in utero* deaths, or whether the child was liveborn or died *in utero*.

Pathology results showed that early spontaneous abortions and IUGR were significantly associated with a higher intensity of fibrin deposits (Table 4). The diffuse or multifocal distribution of the histiocytes did not appear to be associated with any of the unfavorable pregnancy outcomes that we studied, although the deposits appeared less intense in the *in utero* deaths ($p < 0.05$).

4. Discussion

Chronic histiocytic intervillositis of unknown etiology is a rare and poorly understood disease. Our series showed that it is often discovered in patients with severe obstetric complications: early spontaneous abortions, late abortions, preterm deliveries, severe IUGR, and *in utero* deaths. We observed a very substantial rise in ALP levels in more than half the cases in which we performed the assay during pregnancy and found that the intensity of fibrin deposits was associated with higher than expected rates of early spontaneous abortion and IUGR.

Our study is retrospective and inevitably subject to the possibility of recruitment bias. That is, many pathology tests were requested because of the obstetric complications, a factor that obviously limits the interpretation of the associations we observed. The greatest bias certainly involves the *in utero* deaths, since some placental examinations were performed in conjunction with a fetal autopsy. This may partly explain the high rate of such deaths observed here (46.2%) as well as the CIUE prevalence, which is

Table 4
Microscopy: Fetal outcome according to intensity of CIUE lesions, their distribution, and the intensity of fibrin deposits.

	N° patients (denominator)	Spontaneous early abortions ≤12 weeks	*p*	Spontaneous late abortions 13–22 weeks:	*p*	IUD among the children ≥22 weeks	*p*	IUGR ≤ 3rd percentile among the children ≥22 weeks	*p*
Intensity of fibrin deposits									
Low	27	0 (0.0)	< 0.001	6 (22.2)	NS	8 (38.1)	NS	10 (47.6)	=0.05
Moderate	31	15 (48.4)		3 (9.7)		6 (46.1)		10 (76.0.9)	
Elevated	11	6 (54.5)		0 (0.0)		4 (80.0		4 (80.0)	
Distribution of CIUE									
Diffuse	36	8 (22.2)	NS	5 (13.9)	NS	9 (39.1)	NS	15 (65.2)	NS
Multifocal	33	13 (39.4)		4 (12.1)		9(56.3)		9 (56.3)	
CIUE intensity									
Low	18	7 (38.9)	NS	1 (5.6)	NS	8 (80.0)	NS	4 (40.0)	NS
Moderate	37	9 (24.3)		7 (18.9)		6 (28.6)		13 (63.6)	
Elevated	14	5 (35.7)		1 (17.1)		4 (50.0)		7 (87.5)	

CIUE distribution: Diffuse: clusters of histiocyte in most of the intervillous space, magnification × 100. Multifocal clusters of histiocyte scattered throughout the intervillous spaces, variable between microscopic fields.
CIUE intensity: low: clusters of several histiocytes, moderate: less voluminous clusters, elevated: clusters of histiocytes filling the intervillous space.
Intensity of fibrin deposits: low: several scattered deposits, moderate: irregular deposits, elevated: deposits filling the intervillous space in numerous fields.

approximately 10 times greater in our series (0.8%) than in that published by Labarrere and Mullen (0.06%) [1]. Nonetheless, these biases are difficult to avoid [1,2,7,8,11]. Except for Redline [9] no published study of CIUE has involved the routine examination of all placentas from all pregnancies, including those with normal outcomes. It is really difficult to examine all placentas in a referral center as ours, which receives cases from several hospitals.

Some authors have suggested that intervillositis lesions might be confused with the placental lesions observed in women with malaria, listeriosis, tularemia, coccidiomycosis, CMV infection, herpes, psittacosis, cryptococcosis, blastomycosis, rickettsiosis or genitourinary schistosomiasis. The intervillous inflammatory infiltrate in these infections is more polymorphous (polynuclear cells, CD3+ T lymphocytes, eosinophils, cytomegalic inclusion bodies, and malarial pigment) and is often associated with villous lesions [1,2,8,12]. It is highly unlikely that our patients had any of these diseases, given that neither the detailed histories taken nor any of the laboratory tests showed any evidence of an infectious cause. On the other hand, the typical appearance of the mononuclear cell infiltrate filling the intervillous space was systematically verified by CD68 antibody labelling.

The mechanism by which histiocytic intervillositis occurs is not known, articles about it are sparse, and the series small [1–3,7,8,11]. Some authors [12–14] suggest that a "graft rejection" type of reaction might be the mechanism responsible for intervillositis lesions, that is, a maternal immune reaction may be directed against the paternal antigens of the fetus, mediated by the maternal mononuclear cells in the intervillous space, principally histiocytes [4,5]. This immune aggression may occur because of the failure of regulatory mechanisms that should protect the pregnancy throughout gestation [2,8]. In our series, only three patients had an autoimmune disease before pregnancy. Immunological workups were performed for all the women but did not identify any other cases of autoimmune disease; nonetheless, this does not rule out a potential immunologic cause.

These perivillous fibrin deposits are produced by maternal blood when the syncytiotrophoblast is defective, to cover the damaged villous areas [15]. This is a normal phenomenon: it is found in all placentas and increases with gestational age [15]. It is abnormal only in the case of massive deposits or if they are localized in the area of the basal plate [14]. In these cases, they endanger fetal growth and survival by substantially blocking maternofetal exchanges [15]. Our study also found a high percentage of early spontaneous abortions, *in utero* deaths, and severe IUGR when intense fibrin deposits filled the intervillous space.

In our study, ALP levels were high in more than the half the cases. ALP are glycoproteins synthesized by different organs (placenta, bones, intestines, liver, and kidneys). In the placenta, they are principally synthesized by cells in the syncytiotrophoblast [16,17]. Their levels increase physiologically during pregnancy, with the upper limit of normal set at 2.5 times the nonpregnancy normal level. In our study, their origin was sought and confirmed in only three of 18 cases, but was probably placental, given that none of the patients with elevated ALP concentrations had any bone, intestinal, liver, or kidney disease. Otherwise, in our series, eight patients with very elevated ALP levels had severe IUGR ≤ third percentile (the other two ranked between the third and tenth percentiles). Data from the literature about placental ALP levels during pregnancies complicated by IUGR usually report reduced serum ALP levels [16–18] related to placental insufficiency, of which IUGR is the consequence [17]. Accordingly, the high ALP concentrations observed in our study may be related to the syncytial lesions observed in histiocytic intervillositis of unknown etiology. This hypothesis is confirmed in part by the fact that fibrin deposits of moderate to high intensity were present much more often when ALP was very elevated (90.0% vs 50.0%, $p = 0.1$; data not shown). Overall, we propose that the mechanism of histiocytic intervillositis of unknown etiology may be based on an immune phenomenon of an unknown nature that causes histiocytes to flow into the intervillous space, lesions to occur in the syncytial cells, maternal release of ALP by the injured syncytiotrophoblast, and finally syncytial coverage by fibrin deposits that progressively impair maternofetal exchanges (Fig. 2).

The Doppler anomalies of the uterine arteries found in 40.0% of the cases of intervillositis in our series indicate that a vascular phenomenon plays a role in the onset of these complications. Some authors [1,3] have also reported atheromatous lesions of the decidual placental vessels associated with CIUE lesions, as seen in preeclampsia [14]. The frequency of preeclampsia in our study was low (7.7%) and atheromatous lesions were found in only one case, associated with preeclampsia. Accordingly, we stress that the demonstration of abnormal uterine artery Doppler results does not rule out a diagnosis of CIUE.

The *in utero* deaths in our series were associated with the least intense level of intervillositis, as shown by the semi-quantitative assessment of the number of histiocytes in the intervillous space. The younger gestational age at *in utero* death than at live birth in our series may explain this finding. Boyd and Redline showed that the intensity of the histocytic infiltration in intervillositis increased with gestational age [2]. Although we did not find a statistically

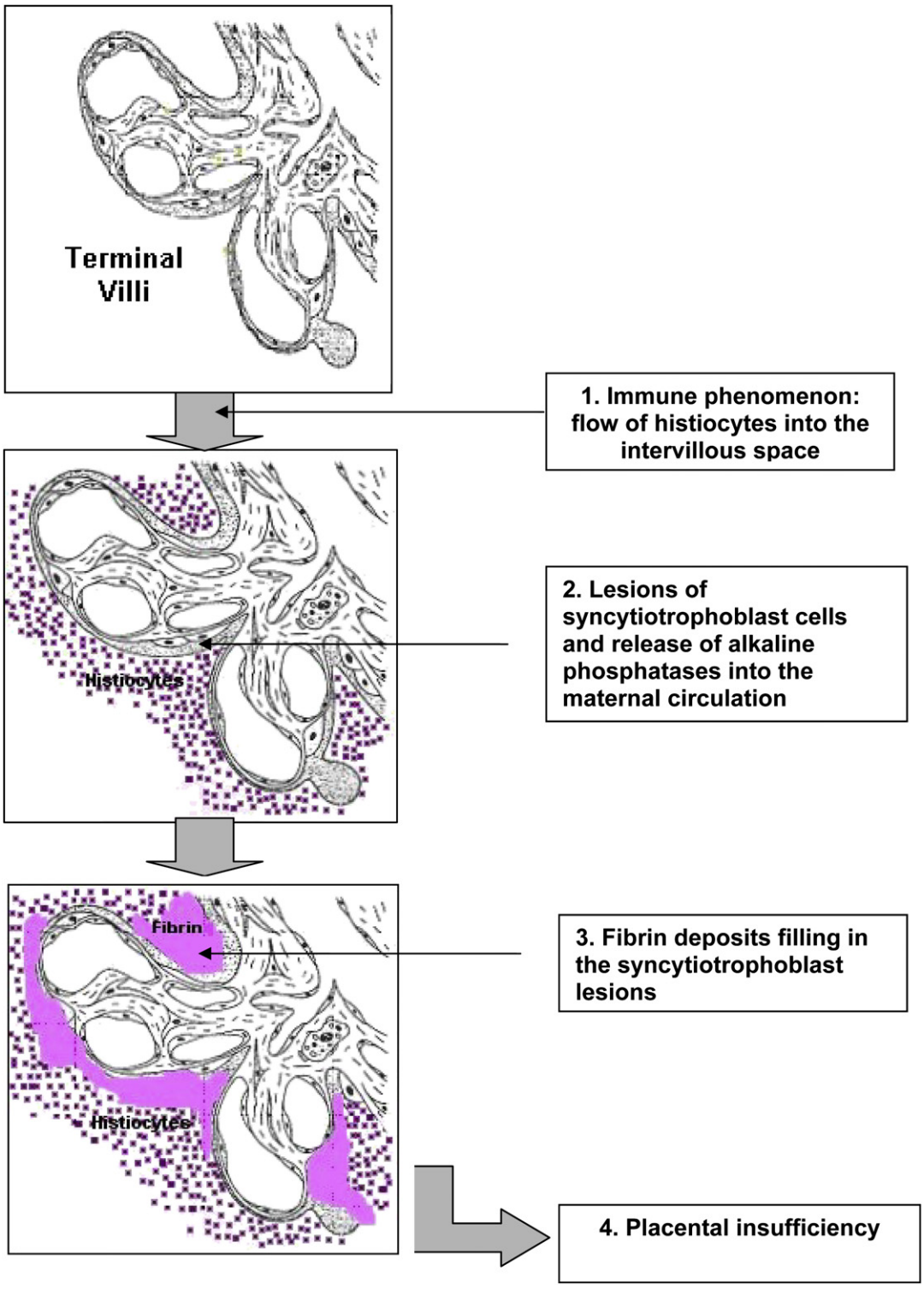

Fig. 2. Pathophysiologic hypothesis of the onset of histiocytic intervillositis. An unexplained immunological phenomenon may lead to the flow of histiocytes from the mother into the intervillous space, then to the degradation of syncytiotrophoblast cells. These lesions cause the release of alkaline phosphatases of syncytial origin into the intervillous space and then into the maternal circulation, before they are covered by fibrin deposits. These deposits may impede the maternofetal exchanges that usually take place across the syncytiotrophoblast, and thus lead to an increased risk of spontaneous abortion, growth restriction, and *in utero* death.

significant linkage between gestational age and intervillositis intensity in our series (data not shown), we hypothesize that this intensity is related more to gestational age than to *in utero* death.

Boyd and Redline [2] estimated the recurrence rate of CIUE at 67.0%. Our study does not allow us to determine its recurrence rate but shows the recurrent nature of some cases, for 9 of 50 patients had recurrences diagnosed at the placental examination (18.0%). These 9 patients had 28 pregnancies with placental histiocytic intervillositis, that is, these women accounted for 40.6% of the CIUE in our series. We underline that these recurrences tended to occur in spontaneous abortions (57.1%) without a significant increase in the number of *in utero* deaths or cases of IUGR. The recurrent character of

intervillositis therefore does not seem to be linked to an aggravation of obstetric complications in the same patient. Moreover, patients with a history of CIUE did not appear to have the same type of recurrences (e.g., spontaneous abortions, *in utero* deaths, or IUGR).

Overall, the associations we studied merit further exploration in future studies. Older studies showed that abnormal increases in placental ALP during pregnancy may precede by two to three weeks the brusque and rapid onset of obstetric complications [16,19]. We plan to assay ALP in the blood of patients with a history of intervillositis, since recurrences are common. If the increase in ALP levels is confirmed, this may be a useful part of prenatal surveillance and monitoring.

Appendix. Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.placenta.2010.11.021

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