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Is chronic histiocytic intervillositis a severe placental disease? A case-control study

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ABSTRACT

Introduction: Chronic histiocytic intervillositis (CHI) is a placental disease that has been associated with unfavorable obstetric outcomes in small, noncomparative series. The objective was to measure the excess risk of adverse obstetric outcomes associated with the discovery of CHI after birth.
Methods: Retrospective single-center case-control study from 2000 through 2016. The case patients had a CHI diagnosis after a pathology analysis of the placenta. Two types of controls were defined for each case: low-risk control women were those who gave birth in our hospital immediately before each case patient, and the high-risk controls were the next women after each case for whom microscopic examination of the placenta was indicated.
Results: We observed 111 cases of CHI during the study period. Compared with the 111 low-risk controls, the cases had a significantly higher frequency of late miscarriages (5.4 vs 0.0%, $p < .03$), small for gestational age (SGA) babies <3rd centile (70.4 vs 0.9%, $p < .001$, OR 140, 95% CI, 19.9–2800), and in utero deaths (35.1 vs 0.9%, $p < .001$, OR 59.6, 95% CI 8.5–1192), with significantly fewer children surviving to discharge (54.9 vs 99.1%, $p < .001$, OR 0.01, 95% CI, 0.00–0.08). All of these factors also differed significantly compared with the high-risk women (severe SGA: OR 3.7, 95% CI 1.9–7.0; in utero death: OR 4.1, 95% CI 1.9–8.7; children surviving to discharge: OR 0.27, 95% CI, 0.14–0.52).
Discussion: Even compared with high-risk pregnancies, CHI is a severe placental disease associated with a substantial excess rate of late miscarriages, severe SGA and in utero death.

1. Introduction

Chronic histiocytic intervillositis (CHI) is a rare placental disease described for the first time by Labarrere and Mullen [1]. It is defined by the presence of histiocytes of maternal origin in the intervillous space, with or without fibrin deposition (Fig. 1). Its incidence is estimated at 0.8%–0.96% among early spontaneous abortions [2,3] and between 0.06% and 0.32% [3,4] of placentas analyzed from the second and third trimesters of pregnancy. The etiology is still unknown but some teams hypothesized an immunopathological disorder with increased Treg lymphocytes in the decidua basalis and the intervillous space [5] and aberrant complement activation [1,6,7].

Despite its rarity, its first descriptions made clear that it is a serious disease with a high risk of adverse outcomes throughout pregnancy: first-trimester miscarriage, in utero death in the second or third trimester, fetal growth restriction (FGR) [2–5,8–12], preeclampsia [10,12], and induced preterm birth [2,9,11,12]. These risks have been found at highly variable rates between studies [2–10]. It is even more difficult to grasp the severity of this placental disease in the absence of comparative studies with control groups. The only comparative study conducted until now showed a more unfavorable prognosis for intervillositis than for villitis [10].

After observing more than 100 cases of CHI at our university hospital center, we sought to assess the severity of this rare disease by measuring

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the excess risk of adverse obstetric outcomes compared with two types of controls: on the one hand, the overall population of women giving birth in our hospital; and on the other hand, those with indications for a pathology examination of the placenta after delivery.

2. Methods

We conducted a retrospective, hospital-based case-control study from January 1, 2000, through December 31, 2016, in our level 3 university hospital maternity ward.

The women included in the case group were those who had a pathology examination of the placenta that diagnosed CHI during the study period; they were ascertained in our computerized database by a code specific for CHI. Among them, 34 women who gave birth at the beginning of the study period (2000–2006) have previously been included in a published study [2]. Women with one or more recurrences of CHI were included each time they had a placenta affected by this disease. This study excludes early miscarriages (gestational age < 14 weeks), twin pregnancies, and medical terminations of pregnancy for severe fetal malformations.

Two type of controls were defined for each case, regardless of their pregnancy outcome: women at low risk were those who gave birth in our hospital immediately before the case women, regardless of whether or not a placental examination was performed. The controls at high risk were the first women immediately after each case for whom microscopic examination of the placenta was indicated.

All examinations were performed by a pathologist specialized in placental diseases. Some examinations have several indications; in decreasing order, the principal indications were: a late miscarriage or in utero death ≥14 weeks, preeclampsia or HELLP syndrome, small for gestational age (SGA) newborns < 3rd percentile [13], and spontaneous preterm delivery between 22 and 36^{+6} weeks. The other indications, less frequent, were combined in a group labeled "other" (unexplained perinatal asphyxia, early premature rupture of membranes, etc.). After macroscopic examination of the placenta, microscopic examination was performed after fixing the tissue with formalin and sampling from healthy areas, cut into 3 paraffin blocks (cord and membranes, central placenta, and peripheral placenta), and from areas that appeared abnormal on visual examination. The paraffin blocks were cut into slices 3 μm thick and stained with hematoxylin-eosin-saffron. CHI was diagnosed when an infiltrate of histiocytic monocytes was found in the intervillous space, with or without fibrin deposition. The histiocytes were systematically confirmed by CD68 immunolabeling (mouse monoclonal antibody, clone PGM1 DakoCytomation ®, dilution 1/1000, pretreated with EDTA buffer, incubation, and DAB staining, Glostrup, Denmark). The characteristics of the intervillositis were also evaluated semi-quantitatively: it was considered "massive" if it affected more than 50% of the intervillous space and "diffuse" when the histiocyte clusters uniformly and massively filled all intervillous spaces at a magnification × 100 [2,4,8]. The presence or absence of fibrin deposition was also noted.

The characteristics of mothers and newborns were collected from the medical files: maternal age, number of previous pregnancies and deliveries (≥22 weeks), ethnicity, active smoking during pregnancy, autoimmune disease confirmed by the presence of at least one type of auto-antibody, and hereditary or acquired thrombophilia. We studied the following events during pregnancy: preeclampsia [14], HELLP syndrome [14,15], cholestasis of pregnancy [16,17], gestational diabetes [18], oligohydramnios (vertical pocket of amniotic fluid < 20 mm), performance of a uterine Doppler scan during the pregnancy (pathological if a resistance index > 0.65 or if a notch — unilateral or bilateral — was observed), performance of an umbilical Doppler in the month before birth (pathological if umbilical resistance was elevated for term or if the cerebroplacental ratio was inverted [19,20]), morphologic anomaly on placental ultrasound, fetal karyotyping, and administration of any of the following treatments during pregnancy: aspirin, low molecular weight heparin (LMWH), or corticosteroids.

To assess some laboratory markers during pregnancy, we collected the following results when they were available: some first- or second-trimester serum markers of trisomy 21, including human chorionic gonadotropin (HCG) and alpha fetoprotein (AFP), as well as the levels of maternal total serum alkaline phosphatases (ALP) (when several values were available, only the latest was considered).

The following pregnancy outcomes were collected: spontaneous late abortion (spontaneous expulsion between 14 and 21^{+6} weeks), in utero death between 14 and 42 weeks, termination of pregnancy after 14 weeks, preterm delivery (defined by birth from 22 to 36^{+6} weeks), live birth ≥ 22 weeks, severe SGA < 3rd percentile at birth [13], and in-hospital neonatal death. Perinatal deaths included in utero death ≥22 weeks, medical termination of pregnancy and in-hospital neonatal death. The especially severe nature of some of the cases of growth restriction led us to calculate the weight Z score for each newborn delivered ≥22 weeks.

The data were recorded and analyzed with Epi Info software (Version 3.1, Epidata Association, Denmark). This data collection was reported as required by French law to the National Data Protection Authority (CNIL) DEC16-406. The Chi-2 test was used to compare percentages. The data for any groups including especially few subjects were reorganized (and the cells pooled), and the comparisons tested with Fisher's exact test. The Kruskal-Wallis nonparametric test was used to search quantitative differences between groups. Percentages are reported between parentheses, and means with the standard deviation of the distribution or with the interquartile range (IQR) 25–75 between square brackets. The odds ratios are reported with their 95% confidence intervals [95% CI]. Differences were considered significant when the p value was <.05.

3. Results

During the study period, our hospital managed 84,681 pregnancy outcomes at or after 14 weeks of gestation; they led to 7955 microscopic

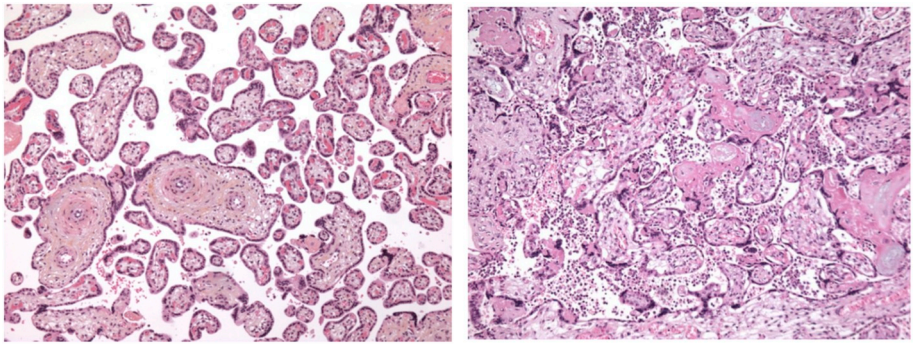

Fig. 1. Histological comparison between normal placenta (left) and placenta with intervillositis (right).

examinations of the placenta (9.4%) (Fig. 2). Among them, 120 had signs of CHI (1.5% of the placental examinations, 0.14% of the births ≥ 14 weeks). Six were excluded as terminations of pregnancy for severe fetal malformations and 3 as twin pregnancies. Our study therefore includes 111 cases of CHI, with which we compared 111 controls at low risk and 111 at high risk. Among these 111 placentas with CHI, 39 were massive (35.1%), 42 diffuse (37.8%), and 51 presented fibrin deposition (45.9%).

Reasons for the placental microscopic examination differed significantly according to study group (Table 1). As expected, few patients had placental examination in low-risk control group. In all groups, most of the examinations were motivated by the observation of SGA at birth. The next most common reason differed between groups; in utero death was more frequent in case group whereas it was preeclampsia and spontaneous preterm delivery in control groups.

The case women were around 2 years older than the controls (Table 2). The groups did not differ for ethnic origin, smoking during pregnancy, or history of thrombophilia (hereditary or acquired). There was a non-significant trend for more autoimmune diseases among case women: lupus, hypothyroidism, multiple sclerosis, rheumatoid arthritis, autoimmune thrombocytopenia, mixed connective tissue disease, and isolated presence of antiB2-glycoprotein1 antibodies, but no antiphospholipid antibody syndrome. Parity did not differ between the groups, but the women in the case group had more previous pregnancies than the controls. They also had a more frequent history of early miscarriages and of in utero deaths, as well as more frequent late miscarriages than the low-risk control group. Finally, 18% of the women in the case group had a previous history of CHI, while none of the control women did ($p < .001$).

Table 3 reports the clinical and paraclinical data collected during these pregnancies. Among the assays performed to screen for trisomy 21, HCG was slightly lower among the case women than among the high-risk controls. Alpha fetoprotein, on the other hand, was more than twice as high among the cases, equal to or greater than 2.5 MoM among one third of this group. The percentage of women at high risk of trisomy was almost identical in all three groups, but fetal karyotyping was clearly more frequent among the cases than the controls (33.3 vs 5.5 in the low-risk and 18.0% in the high-risk control groups). The frequency of preeclampsia was 9.9% among the cases, higher than among the low-risk control women (1.8%). Ultrasound results showing suspected SGA or FGR fetuses were observed for around two thirds of the cases but only half of the controls at high risk and only 5.5% of those at low risk. Similarly, oligohydramnios and abnormalities of umbilical artery Doppler velocimetry were both more frequent in the case group than among either control group. Finally, total ALP were assayed more often and earlier among cases than controls, and their mean levels were higher in the CHI group (one third had total ALP > 600 IU/L).

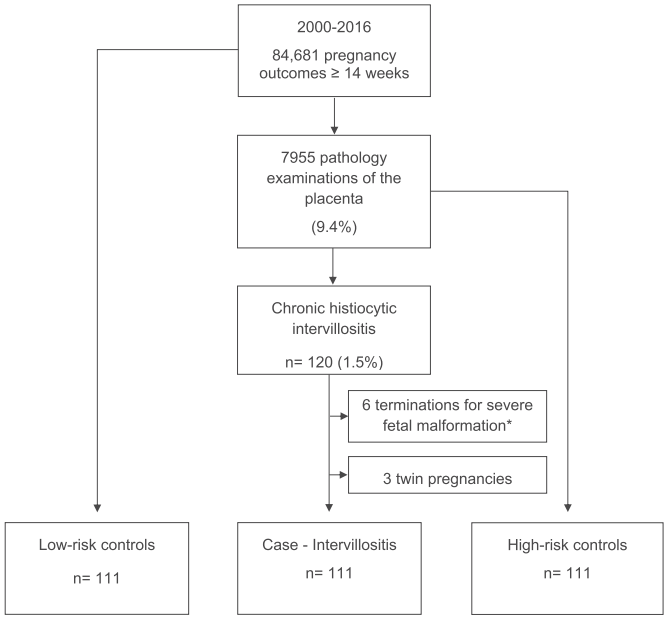

Fig. 2. Flow Chart. * Malformations: 2 major ventriculomegalies, 1 spina bifida, 1 multiple congenital anomalies, 1 hypoplasia of left ventricle, 1 fetal hydrops with bilateral puncture of hydrothorax.

Table 1
Principal reason for placental examination in the different study groups[a].

	[1] Cases (CHI) n = 111	[2] Controls at low risk n = 7	[3] Controls at high risk n = 111	p
Growth restriction at birth	51 (45.9)	4 (57.1)	48 (43.2)	
In utero death (14–42 weeks)	39 (35.1)	1 (14.3)	13 (11.7)	
Preeclampsia/HELLP	11 (9.9)	2 (28.6)	18 (16.2)	**<0.001**
Spontaneous preterm delivery (22–36^{+6} weeks)	3 (2.7)	–	20 (18.0)	
Late miscarriage (14–21^{+6} weeks)	6 (5.4)	–	1 (0.9)	
Other	1 (0.9)	–	11 (9.9)	

[a] When several causes were present, the existence of a late miscarriage or in utero death, regardless of term, prevailed over preeclampsia, which in turn prevailed over growth restriction at birth and spontaneous preterm delivery.

Table 2
Women's characteristics and history, according to group.

	[1] Cases (CHI) n = 111	[2] Controls at low risk n = 111	[1] vs [2] p	[3] Controls a high risk n = 111	[1] vs [3] p
Maternal age (years)	30.8 ± 5.9	28.9 ± 5.5	**0.02**	28.7 ± 5.6	**0.01**
White ethnicity	80 (72.1)	83 (76.1)	0.49	77 (69.4)	0.67
Smoked during pregnancy	16 (14.4)	19 (17.4)	0.54	21 (18.9)	0.37
Hereditary or acquired thrombophilia	2 (1.8)	1 (0.9)	>0.99	2 (1.8)	>0.99
Autoimmune disease	9 (8.1)	3 (2.7)	0.08	3 (2.7)	0.08
Nulliparous	40 (36.0)	53 (47.7)	0.08	50 (45.0)	0.17
Number of previous pregnancies	2.5 [1–4]	1.3 [0–2]	**<0.001**	1.6 [0–2]	**<0.001**
History of early miscarriage <14 weeks	44 (39.6)	21 (19.3)	**<0.001**	29 (26.1)	**0.03**
History of late miscarriage (14–21^{+6})	6 (5.4)	0 (0.0)	**0.03**	2 (1.8)	0.28
History of in utero death	19 (17.1)	3 (2.7)	**<0.001**	3 (2.7)	**<0.001**
History of CHI	20 (18.0)	0 (0.0)	**<0.001**	0 (0.0)	**<0.001**

Pregnancy outcomes are described in Table 4. Compared with the controls at low risk, the cases had a significantly higher rate of late miscarriages (5.4 vs 0.0%, $p < .03$, OR undefined) and in utero deaths (35.1 vs 0.9%, $p < .001$, OR 59.6, 95% CI, 8.5–1192), with a very significantly lower percentage of children born alive after 22 weeks (55.9 vs 99.1%, $p < .001$, OR 0.01, 95% CI 0.00–0.08). These factors differed almost always significantly compared with the women at high risk (late miscarriages: OR 6.3 95% CI 0.73–141; in utero death: OR 4.1, 95% CI 1.9–8.7; live births ≥ 22 weeks: OR 0.23, 95% CI 0.11–0.45).

Table 3
Clinical and paraclinical aspects of pregnancy, by group.

	[1] Cases (CHI) n = 111	[2] Controls at low risk n = 111	[1] vs [2] p	[3] Controls at< high risk n = 111	[1] vs [3] p
HCG in MoM	1.17 ± 0.99	1.37 ± 0.94	0.17	1.55 ± 1.23	**0.02**
≥ 2.5 MoM	3 (5.3)	5 (10.6)	0.46	6 (12.0)	0.30
AFP in MoM	2.1 ± 1.2	0.99 ± 0.36	**<0.001**	1.32 ± 0.69	**0.01**
≥ 2.5 MoM	10 (34.5)	0 (0.0)	**<0.001**	3 (14.3)	0.19
Risk of trisomy 21 > 1/250	8 (12.5)	5 (7.4)	0.32	6 (8.6)	0.46
Performance of fetal karyotyping	37 (33.3)	6 (5.5)	**<0.001**	20 (18.0)	**0.01**
Abnormal karyotype	1 (2.7) [a]	0 (0.0)	>0.99	0 (0.0)	0.53
Gestational diabetes	10 (9.3)	17 (16.7)	0.11	13 (13.1)	0.39
Cholestasis of pregnancy	1 (0.9)	2 (1.8)	>0.99	1 (0.9)	>0.99
Preeclampsia	11 (9.9)	2 (1.8)	**0.01**	19 (17.1)	0.12
with HELLP syndrome	5 (5.3)	0 (0.0)	**0.02**	4 (3.8)	0.74
Estimated fetal weight <10 centile during pregnancy	73 (65.8)	6 (5.5)	**<0.001**	57 (51.3)	**0.03**
Oligohydramnios on ultrasound	47 (42.3)	5 (4.7)	**<0.001**	27 (26.2)	**0.01**
Abnormal uterine Doppler spectrum[b]	36/83 (43.4)	7/17 (36.8)	0.60	28/53 (52.8)	0.28
Abnormal umbilical Doppler spectrum[c]	33/81 (40.7)	2/40 (4.9)	**<0.001**	20/77 (26.0)	**0.05**
Placenta anomaly on ultrasound	7 (6.3)	2 (1.8)	0.17	9 (8.1)	0.60
Assay of total alkaline phosphatases	60 (54.1)	21 (10.3)	**<0.001**	42 (37.8)	**0.02**
Last rate (IU/L)	625 ± 759	242 ± 201	0.05	191 ± 105	**0.002**
Gestational age at last assay (weeks)	28.6 ± 6.7	35.5 ± 4.6	**<0.001**	30.1 ± 6.6	0.22
Rate > 600 IU/L	18 (30.0)	1 (4.8)	**0.01**	0 (0.0)	**<0.001**

[a] Trisomy 16, limited to the placenta.
[b] Mean resistance index ≥0.65 or presence of notch.
[c] Inversion of cerebroplacental ratio or high resistance index.

The percentage of live births ≥22 weeks that were preterm was much higher in the case group than in the low-risk control group (64.5 vs 6.4%, p < .001), and the rate of induced preterm birth was higher among the cases than in either control group. Birth weight was markedly lower in the cases than controls (1500 ± 885 vs 3160 ± 640 in the low-risk and 1945 ± 870 g in the high-risk controls, p < .001). Severe SGA was far more frequent in the case group than in the low risk and the high risk group (70.4 vs 0.9%, p < .001, OR 140, 95% CI, 19.9–2800 and 70.4 vs 39.4%, p < .001, OR 3.7, 95% CI 1.9–7.0, respectively). Even considering only the live births ≥22 weeks, growth restriction was much more severe in the cases than in either control group: 8.1% of the case infants did not reach even – 5.0 standard deviation (vs 0.0% and 1.1% in low- and high-risk control groups, p = .006 and p = .04, respectively).

Finally, perinatal deaths were much more frequent among the cases than among the controls at either low (30.7 vs 0.9%, p < .001, OR 48.7, 95% CI 6.8–986) or high risk (30.7 vs 12.5%, p = .014, OR 3.1, 95% CI 1.4–6.9). The percentage of children discharged home was very significantly lower in the case group than in the low-risk and high-risk groups (54.9 vs 99.1% and 82.0%, p < .001, OR 0.01, 95% CI 0.00–0.08 and OR 0.27, 95% CI 0.14–0.52, respectively).

Among the women receiving specific treatments during pregnancy (Table 5), 18 women in the case group received aspirin (16.2%), 7 LMWH at a preventive dose (6.3%), 6 continuous oral corticosteroids (5.4%), and 90 none of these treatments (81.1%). Table 5 shows no difference in pregnancy outcomes according to the existence or type of treatment.

4. Discussion

By comparing cases simultaneously with low risk and high risk pregnancies, our study showed that the discovery of CHI explains severe complications. It is associated with a rate of severe SGA fetuses and in utero deaths about four times higher than in high-risk pregnancies, resulting in a four-fold reduction in the rate of survivors at discharge.

In our study, CHI is associated with late miscarriages, severe SGA, and in utero deaths. The frequency of severe SGA fetuses in case women was 70%. This rate is higher than the 48% estimated in a recent meta-analysis [21], but the rates were extremely variable between the studies, ranging from 27 to 81% [1–5,8,10,11,22]. In a third of the cases, testing for chromosomal aberrations served as evidence of the early and severe character of the growth restriction. The signs of impaired feto-placental perfusion that we report here have already been described in shorter, non-comparative series: the frequency of oligohydramnios that we measured is the same as that found by Koby et al. (40%) [12], and lower than that reported by others (up to 80% [4,5]). Similarly, the frequency of an abnormal umbilical artery Doppler spectrum was 40% (IC95 30.0–51.4%) in our series, but seemed slightly higher in shorter series: 60% (IC95 36.0–78.3%) in the series by Nowak and al [10]. and 72% (IC95 54.4–89.6%) in that of Koby et al. [12]. Although other authors have reported frequent abnormalities of uterine artery Doppler flows [2,4,12], the comparative nature of our study enabled us to show that the rate of these abnormalities is similar to that observed in controls. These observations tend to support a primarily placental origin for these fetal perfusion disorders.

From a clinical point of view, our study has confirmed that CHI appears to be related to the risk of in utero death, even in comparison with women with placental examinations performed for obstetric indications. This risk of in utero death has been mentioned since the first description of CHI in 1987 by Labarrere and Mullen [1] and then by all the authors before us [2–5,8–11,23,24]. The fact that 17 in utero deaths among 39 (43.6%) occurred before 22 weeks is evidence of the early nature of placental perfusion disorders.

Late miscarriages were observed in 5% of the cases of our study, corresponding to the frequency described by other authors, with rates varying between 0 and 12.5% [4,8–10,12]. The mechanism of these spontaneous expulsions between 14 and 21^{+6} weeks is unknown. In our series, histopathological signs of chorioamnionitis were associated with CHI in three of the six late miscarriages observed in the case group.

Laboratory testing showed that alpha fetoprotein exceeds 2.5 MoM in more than a third of the women with CHI. Early and severe abnormalities of placental perfusion are already known to be one of the causes of this elevation, via the leakage of plasma from the fetal compartment toward the intervillous space drained by the mother [25]. Finally, the assay of total serum ALP was available for half the cases and was substantially elevated in a third of them (>600 IU/L). This high level was found among 10 of the 18 women in our previous series [2]; it was confirmed among 8 of the 42 new women in our sample, for a total of 18 women with elevated total ALP among the 60 case women who had this assay (30.0%). Another team recently reported this same 30% rate [12]. The comparative nature of our study indicates that this is a significantly high level, although it concerns only one third of the women with CHI at the threshold of 600 IU/L. We previously showed the placental origin of the high ALP level and suggested a mechanism by which these enzymes are released by the syncytiotrophoblast, which synthesizes them in the

Table 4
Pregnancy outcomes according to group.

	[1] Cases (CHI) n = 111	[2] Controls at low risk n = 111	[1] vs [2] p	OR [95% CI]	[3] Controls at n = 111	[1] vs [3] p	OR [95% CI]
Late miscarriage (14–21^{+6})	6 (5.4)	0 (0.0)	**0.03**	Undefined	1 (0.9)	0.12	6.3 [0.73–141]
Termination of pregnancy [a]	4 (4.5)	0 (0.0)	0.12		3 (2.7)	>0.99	
In utero death 14–42 weeks	39 (35.1)	1 (0.9)	**<0.001**	59.6 [8.5–1192]	13 (11.7)	**<0.001**	4.1 [1.9–8.7]
14–21^{+6}	17 (15.3)	0 (0.0)	**<0.001**	Undefined	6 (5.4)	**0.015**	3.2 [1.1–9.4]
22–42	22 (19.8)	1 (0.9)	**<0.001**	27.2 [3.4–550]	7 (6.3)	**0.003**	3.7 [1.4–10.0]
Gestational age at delivery [b]	33.6 ± 4.7	39.4 ± 2.6	**<0.001**		35.1 ± 5.0	**0.024**	
22–27^{+6} weeks	13 (14.7)	2 (1.8)			12 (11.5)		
28–36^{+6} weeks	50 (56.8)	6 (5.4)	**<0.001**		45 (43.3)	**0.06**	
> 37 weeks	25 (28.4)	103 (92.8)			47 (45.2)		
Live birth ≥ 22 weeks	62 (55.9)	110 (99.1)	**<0.001**	0.01 [0.0–0.08]	94 (84.7)	**<0.001**	0.23 [0.11–0.45]
Preterm birth [c]	40 (64.5)	7 (6.4)	**<0.001**	26.8 [9.8–75.9]	48 (51.1)	0.10	1.74 [0.86–3.6]
Spontaneous	4 (6.4)	2 (1.8)	0.19	3.7 [0.56–30.3]	9 (9.6)	0.49	0.65 [0.16–2.5]
Induced	36 (58.1)	5 (4.5)	**<0.001**	29.1 [9.6–94.2]	39 (41.5)	0.05	2.0 [0.97–4.0]
Birth weight (grams)[b]	1500 ± 885	3160 ± 640	**<0.001**		1945 ± 870	**<0.001**	
< 1500	43 (48.9)	3 (2.7)			35 (33.7)		
1500–2499	35 (39.8)	6 (5.4)	**<0.001**		37 (35.6)	**0.004**	
> 2500	10 (11.4)	102 (91.9)			32 (30.8)		
SGA < 3rd percentile ≥ 22 weeks[b]	62 (70.4)	1 (0.9)	**<0.001**	140 [19.9–2800]	41 (39.4)	**<0.001**	3.7 [1.9–7.0]
Birthweight expressed as z score[b]	−3.0 ± 2.4	0.54 ± 1.4	**<0.001**		−1.4 ± 1.8	**<0.001**	
Z score < - 4.0	27 (30.7)	2 (1.8)	**<0.001**		11 (10.6)	**<0.001**	
Z score < - 5.0	18 (20.5)	1 (0.9)	**<0.001**		3 (2.9)	**<0.001**	
Llve births only[c]	−2.7 ± 1.6	0.6 ± 1.3	**<0.001**		−1.4 ± 1.8	**<0.001**	
Zscore < - 4.0	14 (22.6)	1 (0.9)	**<0.001**		8 (8.6)	**0.016**	
Zscore < - 5.0	5 (8.1)	0 (0.0)	**0.006**		1 (1.1)	**0.04**	
Cesarean section[c]	40 (64.5)	21 (19.1)	**<0.001**	2.41 [1.3–4.5]	54 (57.4)	0.38	1.4 [0.66–2.8]
In-hospital neonatal death	1 (1.6)	0 (0.0)	>0.99		3 (3.2)	>0.99	
Perinatal death (≥22 wks - in-hospital)[b]	27 (30.7)	1 (0.9)	**<0.001**	48.7 [6.8–986]	13 (12.5)	**0.014**	3.1 [1.4–6.9]
Survived to discharge home	61 (54.9)	110 (99.1)	**<0.001**	0.01 [0.0–0.08]	91 (82.0)	**<0.001**	0.27 [0.14–0.52]

[a] The 7 terminations were performed ≥ 22 weeks including 6 for severe fetal growth restriction.
[b] Births ≥ 22 weeks, live-born child or not.
[c] Births ≥ 22 weeks, live born only.

Table 5
Pregnancy outcome according to treatment in case women. Women with more than one treatment are counted once for each type of treatment during each pregnancy.

	Aspirin n = 18 (16.2)	LMWH n = 7 (6.3)	Corticosteroids n = 6 (5.4)	None of these treatments n = 90 (81.1)	p
Outcome ≥ 22 weeks	15 (83.3)	7 (100.0)	6 (100.0)	70 (77.8)	0.12
Live birth ≥ 22 weeks	9 (50.0)	4 (57.1)	3 (50.0)	51 (56.7)	0.87
Weight if live born (g)	1680 ± 585	1755 ± 516	1670 ± 655	1640 ± 750	0.93
SGA < 3rd percentile ≥ 22 weeks [a]	10/15 (66.7)	6/7 (85.7)	3/6 (50.0)	49/70 (70.0)	0.84
Birthweight expressed as z score [a]	- 3.53 ± 2.5	- 4.06 ± 2.59	- 2.74 ± 2.57	- 3.16 ± 2.9	0.74
Gestational age if live born (weeks)	34.2 [32.0–36.4]	34.7 [33.3–35.6]	34.1 [32.7–36.0]	34.4 [31.1–38.2]	0.90
Survived to discharge home	9 (50.0)	4 (57.1)	3 (50.0)	50 (55.6)	0.90

[a] Births ≥ 22 weeks, live-born child or not.

placenta [2].

Our work has limitations due to selection bias simultaneously among the cases and the controls. For the case group, the placental examinations that revealed the existence of CHI are almost always performed because of the onset of obstetric complications. On the one hand, this indication bias certainly resulted in a strong overestimation of the risks linked to CHI. On the other hand, nonetheless, it was identical in the women at high risk, thus demonstrating the especially severe prognosis for CHI. Inversely, among the control women at low risk, the lack of a pathology examination might have masked the presence of CHI with a favorable outcome. It is moreover probable that we underestimated the number of placentas with CHI during the study period, during which slightly less than 10% of the placentas were examined. No study can overcome this weakness, because it is simply not practicable to examine all placentas to determine the frequency of their rare microscopic diseases. If we assume that none of the non-examined placentas showed CHI, its frequency in our sample was 1/700 births in the second and third trimesters (0.14%), compatible with the rates measured by other authors with the same limitation (between 1/300 and 1/1600) [3,4]. Finally, the difficulty of accurately counting all pregnancy outcomes before 14 weeks led us to exclude first-trimester miscarriages from our study, although numerous authors have reported an association between intervillositis and early miscarriage [2–5,8,11,21,22]. Our study nonetheless found a significantly higher rate of women with a history of

first-trimester miscarriages among the cases than the controls and thus confirms the existence of this association.

Our study gave us the opportunity to examine fetal outcomes according to the existence of treatment during pregnancy for women with CHI. Even though the small number of individuals treated limits our results, none of the analyses performed suggests any benefit from any of these treatments, whether they are low-dose aspirin, preventive doses of LMWH, or oral corticosteroids. These results are consistent with those by Contro et al. [26], who found no evidence supporting the use of these treatments in their compilation of published CHI cases. Nevertheless, although the diagnosis of CHI can only be done after birth, further pregnancies should be considered at high obstetrical risk due to a high recurrence risk of CHI. A sonographic and cardiotocographic watch should be performed in shorter intervalls in order to monitor fetal growth and to avoid in utero death.

Finally, our study has objectively confirmed the severity of the obstetric complications associated with CHI. Late miscarriages, in utero deaths, and FGR can therefore reasonably be attributed to CHI when this diagnosis is made after microscopic examination of the placenta. In view of the high risk of recurrence, CHI appears without doubt one of the most severe placental diseases.

Declaration of competing interest

The authors report no conflict of interest.

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