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### ► To cite this version:

C. Homatter, Morgane Stichelbout, Louise Devisme, A. Chudzinski, V. Debarge, et al.. Is chronic histiocytic intervillitis a severe placental disease? a case-control study. *Placenta*, 2020, *Placenta*, 91, pp.31-36. 10.1016/j.placenta.2019.12.020 . hal-04512837

**HAL Id: hal-04512837**

**<https://hal.univ-lille.fr/hal-04512837v1>**

Submitted on 29 Nov 2024

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1 **Is chronic histiocytic intervillitis a severe placental disease? a**  
2 **case-control study**

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28 Declarations of interest: none

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29 **Abstract**

30 **Introduction**

31 Chronic histiocytic intervillitis (CHI) is a placental disease that has been associated  
32 with unfavorable obstetric outcomes in small, noncomparative series. The objective  
33 was to measure the excess risk of adverse obstetric outcomes associated with the  
34 discovery of CHI after birth.

35 **Methods**

36 Retrospective single-center case-control study from 2000 through 2016. The case  
37 patients had a CHI diagnosis after a pathology analysis of the placenta. Two types of  
38 controls were defined for each case: low-risk control women were those who gave birth  
39 in our hospital immediately before each case patient, and the high-risk controls were  
40 the next women after each case for whom microscopic examination of the placenta  
41 was indicated.

42 **Results**

43 We observed 111 cases of CHI during the study period. Compared with the 111 low-  
44 risk controls, the cases had a significantly higher frequency of late miscarriages (5.4  
45 vs 0.0%,  $p < .03$ ), small for gestational age (SGA) babies  $<3^{\text{rd}}$  centile (70.4 vs 0.9%,  
46  $p < 0.001$ , OR 140, 95% CI, 19.9–2800), and in utero deaths (35.1 vs 0.9%,  $p < .001$ ,  
47 OR 59.6, 95% CI 8.5-1192), with significantly fewer children surviving to discharge  
48 (54.9 vs 99.1%,  $p < .001$ , OR 0.01, 95% CI, 0.00–0.08). All of these factors also differed  
49 significantly compared with the high-risk women (severe SGA: OR 3.7, 95% CI 1.9–  
50 7.0; in utero death: OR 4.1, 95% CI 1.9-8.7; children surviving to discharge: OR 0.27,  
51 95% CI, 0.14-0.52).

52 **Discussion**

53 Even compared with high-risk pregnancies, CHI is a severe placental disease  
54 associated with a substantial excess rate of late miscarriages, severe SGA and in utero  
55 death.

56

57 **Keywords**

58 Placenta Diseases; Pregnancy Outcome; Comparative Study; Fetal Death; Fetal  
59 Growth Retardation, Small for Gestational Age

# 1 Introduction

2

3 Chronic histiocytic intervillitis (CHI) is a rare placental disease described for the  
4 first time by Labarrere and Mullen (1). It is defined by the presence of histiocytes of  
5 maternal origin in the intervillous space, with or without fibrin deposition (Figure 1). Its  
6 incidence is estimated at 0.8% to 0.96% among early spontaneous abortions (2,3)  
7 and between 0.06% and 0.32% (3,4) of placentas analyzed from the second and  
8 third trimesters of pregnancy. The etiology is still unknown but some teams  
9 hypothesized an immunopathological disorder with increased Treg lymphocytes in  
10 the decidua basalis and the intervillous space (5) and aberrant complement activation  
11 (1,6,7).

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

20 After observing more than 100 cases of CHI at our university hospital center, we  
21 sought to assess the severity of this rare disease by measuring the excess risk of  
22 adverse obstetric outcomes compared with two types of controls: on the one hand,  
23 the overall population of women giving birth in our hospital; and on the other hand,  
24 those with indications for a pathology examination of the placenta after delivery.

## 25 **Methods**

26

27 We conducted a retrospective, hospital-based case-control study from January 1,  
28 2000, through December 31, 2016, in our level 3 university hospital maternity ward.

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

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

42 All examinations were performed by a pathologist specialized in placental diseases.  
43 Some examinations have several indications; in decreasing order, the principal  
44 indications were: a late miscarriage or in utero death  $\geq$  14 weeks, preeclampsia or  
45 HELLP syndrome, small for gestational age (SGA) newborns < 3<sup>rd</sup> percentile (13),  
46 and spontaneous preterm delivery between 22 and 36<sup>+6</sup> weeks. The other  
47 indications, less frequent, were combined in a group labeled "other" (unexplained  
48 perinatal asphyxia, early premature rupture of membranes, etc.). After macroscopic  
49 examination of the placenta, microscopic examination was performed after fixing the

50 tissue with formalin and sampling from healthy areas, cut into 3 paraffin blocks (cord  
51 and membranes, central placenta, and peripheral placenta), and from areas that  
52 appeared abnormal on visual examination. The paraffin blocks were cut into slices 3  
53  $\mu\text{m}$  thick and stained with hematoxylin-eosin-saffron. CHI was diagnosed when an  
54 infiltrate of histiocytic monocytes was found in the intervillous space, with or without  
55 fibrin deposition. The histiocytes were systematically confirmed by CD68  
56 immunolabeling (mouse monoclonal antibody, clone PGM1 DakoCytomation  $\text{\textcircled{R}}$ ,  
57 dilution 1/1000, pretreated with EDTA buffer, incubation, and DAB staining, Glostrup,  
58 Denmark). The characteristics of the intervillositis were also evaluated semi-  
59 quantitatively: it was considered "massive" if it affected more than 50% of the  
60 intervillous space and "diffuse" when the histiocyte clusters uniformly and massively  
61 filled all intervillous spaces at a magnification  $\times 100$  (2,4,8). The presence or absence  
62 of fibrin deposition was also noted.

63 The characteristics of mothers and newborns were collected from the medical files:  
64 maternal age, number of previous pregnancies and deliveries ( $\geq 22$  weeks), ethnicity,  
65 active smoking during pregnancy, autoimmune disease confirmed by the presence of  
66 at least one type of auto-antibody, and hereditary or acquired thrombophilia. We  
67 studied the following events during pregnancy: preeclampsia (14), HELLP syndrome  
68 (14,15), cholestasis of pregnancy (16,17), gestational diabetes (18), oligohydramnios  
69 (vertical pocket of amniotic fluid  $< 20$  mm), performance of a uterine Doppler scan  
70 during the pregnancy (pathological if a resistance index  $> 0.65$  or if a notch —  
71 unilateral or bilateral — was observed), performance of an umbilical Doppler in the  
72 month before birth (pathological if umbilical resistance was elevated for term or if the  
73 cerebroplacental ratio was inverted (19,20)), morphologic anomaly on placental

74 ultrasound, fetal karyotyping, and administration of any of the following treatments  
75 during pregnancy: aspirin, low molecular weight heparin (LMWH), or corticosteroids.

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

81 The following pregnancy outcomes were collected: spontaneous late abortion  
82 (spontaneous expulsion between 14 and 21<sup>+6</sup> weeks), in utero death between 14 and  
83 42 weeks, termination of pregnancy after 14 weeks, preterm delivery (defined by birth  
84 from 22 to 36<sup>+6</sup> weeks), live birth  $\geq$  22 weeks, severe SGA  $<$  3<sup>rd</sup> percentile at birth  
85 (13), and in-hospital neonatal death. Perinatal deaths included in utero death  $\geq$  22  
86 weeks, medical termination of pregnancy and in-hospital neonatal death. The  
87 especially severe nature of some of the cases of growth restriction led us to calculate  
88 the weight Z score for each newborn delivered  $\geq$  22 weeks.

89

90 The data were recorded and analyzed with Epi Info software (Version 3.1, Epidata  
91 Association, Denmark). This data collection was reported as required by French law  
92 to the National Data Protection Authority (CNIL) DEC16-406. The Chi-2 test was  
93 used to compare percentages. The data for any groups including especially few  
94 subjects were reorganized (and the cells pooled), and the comparisons tested with  
95 Fisher's exact test. The Kruskal-Wallis nonparametric test was used to search  
96 quantitative differences between groups. Percentages are reported between  
97 parentheses, and means with the standard deviation of the distribution or with the



98 interquartile range (IQR) 25-75 (between square brackets). The odds ratios are  
99 reported with their 95% confidence intervals [95% CI]. Differences were considered  
100 significant when the p value was  $< 0.05$ .

101

## 102 **Results**

103

104 During the study period, our hospital managed 84,681 pregnancy outcomes at or  
105 after 14 weeks of gestation; they led to 7955 microscopic examinations of the  
106 placenta (9.4%) (Figure 2). Among them, 120 had signs of CHI (1.5% of the placental  
107 examinations, 0.14% of the births  $\geq$  14 weeks). Six were excluded as terminations of  
108 pregnancy for severe fetal malformations and 3 as twin pregnancies. Our study  
109 therefore includes 111 cases of CHI, with which we compared 111 controls at low risk  
110 and 111 at high risk. Among these 111 placentas with CHI, 39 were massive  
111 (35.1%), 42 diffuse (37.8%), and 51 presented fibrin deposition (45.9%).

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

118 The case women were around 2 years older than the controls (Table 2). The groups  
119 did not differ for ethnic origin, smoking during pregnancy, or history of thrombophilia  
120 (hereditary or acquired). There was a non-significant trend for more autoimmune  
121 diseases among case women: lupus, hypothyroidism, multiple sclerosis, rheumatoid  
122 arthritis, autoimmune thrombocytopenia, mixed connective tissue disease, and  
123 isolated presence of antiB2-glycoprotein1 antibodies, but no antiphospholipid  
124 antibody syndrome. Parity did not differ between the groups, but the women in the  
125 case group had more previous pregnancies than the controls. They also had a more

126 frequent history of early miscarriages and of in utero deaths, as well as more  
127 frequent late miscarriages than the low-risk control group. Finally, 18% of the women  
128 in the case group had a previous history of CHI, while none of the control women did  
129 ( $p < .001$ ).

130 Table 3 reports the clinical and paraclinical data collected during these pregnancies.  
131 Among the assays performed to screen for trisomy 21, HCG was slightly lower  
132 among the case women than among the high-risk controls. Alpha fetoprotein, on the  
133 other hand, was more than twice as high among the cases, equal to or greater than  
134 2.5 MoM among one third of this group. The percentage of women at high risk of  
135 trisomy was almost identical in all three groups, but fetal karyotyping was clearly  
136 more frequent among the cases than the controls (33.3 vs 5.5 in the low-risk and  
137 18.0% in the high-risk control groups). The frequency of preeclampsia was 9.9%  
138 among the cases, higher than among the low-risk control women (1.8%). Ultrasound  
139 results showing suspected SGA or FGR fetuses were observed for around two thirds  
140 of the cases but only half of the controls at high risk and only 5.5% of those at low  
141 risk. Similarly, oligohydramnios and abnormalities of umbilical artery Doppler  
142 velocimetry were both more frequent in the case group than among either control  
143 group. Finally, total ALP were assayed more often and earlier among cases than  
144 controls, and their mean levels were higher in the CHI group (one third had total ALP  
145  $> 600$  IU/L).

146 Pregnancy outcomes are described in Table 4. Compared with the controls at low  
147 risk, the cases had a significantly higher rate of late miscarriages (5.4 vs 0.0%,  $p <$   
148  $.03$ , OR undefined) and in utero deaths (35.1 vs 0.9%,  $p < .001$ , OR 59.6, 95% CI,  
149 8.5-1192), with a very significantly lower percentage of children born alive after 22  
150 weeks (55.9 vs 99.1%,  $p < .001$ , OR .01, 95% CI 0.00–0.08). These factors differed

151 almost always significantly compared with the women at high risk (late miscarriages:  
152 OR 6.3 95% CI 0.73-141; in utero death: OR 4.1, 95% CI 1.9 -8.7; live births  $\geq$  22  
153 weeks: OR 0.23, 95% CI 0.11–0.45).

154 The percentage of live births  $\geq$  22 weeks that were preterm was much higher in the  
155 case group than in the low-risk control group (64.5 vs 6.4%,  $p < .001$ ), and the rate  
156 of induced preterm birth was higher among the cases than in either control group.  
157 Birth weight was markedly lower in the cases than controls ( $1500 \pm 885$  vs  $3160 \pm$   
158  $640$  in the low-risk and  $1945 \pm 870$  g in the high-risk controls,  $p < .001$ ). Severe SGA  
159 was far more frequent in the case group than in the low risk and the high risk group  
160 (70.4 vs 0.9%,  $p < .001$ , OR 140, 95% CI, 19.9–2800 and 70.4 vs 39.4%,  $p < .001$ , OR  
161 3.7, 95% CI 1.9–7.0, respectively ). Even considering only the live births  $\geq$  22 weeks,  
162 growth restriction was much more severe in the cases than in either control group:  
163 8.1% of the case infants did not reach even  $-5.0$  standard deviation (vs 0.0% and  
164 1.1% in low- and high-risk control groups,  $p = .006$  and  $p = .04$ , respectively).

165 Finally, perinatal deaths were much more frequent among the cases than among the  
166 controls at either low (30.7 vs 0.9%,  $p < 0.001$ , OR 48.7, 95% CI 6.8-986) or high  
167 risk (30.7 vs 12.5%,  $p = .014$ , OR 3.1, 95% CI 1.4-6.9). The percentage of children  
168 discharged home was very significantly lower in the case group than in the low-risk  
169 and high-risk groups (54.9 vs 99.1% and 82.0%,  $p < .001$ , OR 0.01, 95% CI 0.00-  
170 0.08 and OR 0.27, 95% CI 0.14-0.52, respectively).

171 Among the women receiving specific treatments during pregnancy (Table 5), 18  
172 women in the case group received aspirin (16.2%), 7 LMWH at a preventive dose  
173 (6.3%), 6 continuous oral corticosteroids (5.4%), and 90 none of these treatments

174 (81.1%). Table 5 shows no difference in pregnancy outcomes according to the  
175 existence or type of treatment.

176

## 177 **Discussion**

178

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

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

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

208 Late miscarriages were observed in 5% of the cases of our study, corresponding to  
209 the frequency described by other authors, with rates varying between 0 and 12.5%  
210 (4,8–10,12) . The mechanism of these spontaneous expulsions between 14 and 21<sup>+6</sup>  
211 weeks is unknown. In our series, histopathological signs of chorioamnionitis were  
212 associated with CHI in three of the six late miscarriages observed in the case group.

213 Laboratory testing showed that alpha fetoprotein exceeds 2.5 MoM in more than a  
214 third of the women with CHI. Early and severe abnormalities of placental perfusion  
215 are already known to be one of the causes of this elevation, via the leakage of  
216 plasma from the fetal compartment toward the intervillous space drained by the  
217 mother (25). Finally, the assay of total serum ALP was available for half the cases  
218 and was substantially elevated in a third of them (> 600 IU/L). This high level was  
219 found among 10 of the 18 women in our previous series (2); it was confirmed among  
220 8 of the 42 new women in our sample, for a total of 18 women with elevated total ALP  
221 among the 60 case women who had this assay (30.0%). Another team recently  
222 reported this same 30% rate (12). The comparative nature of our study indicates that  
223 this is a significantly high level, although it concerns only one third of the women with  
224 CHI at the threshold of 600 IU/L. We previously showed the placental origin of the

225 high ALP level and suggested a mechanism by which these enzymes are released by  
226 the syncytiotrophoblast, which synthesizes them in the placenta (2).

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



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

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

265

266 **Acknowledgements**

267

268 The authors thank Dr. Louise Devisme (Director of Pathology, Lille **Center** for  
269 histopathological) for her expert histopathological evaluation of chronic histiocytic  
270 intervillitis and for iconography. They also thank Ms Jo Ann Cahn for language  
271 help.

272

273 This research did not receive any specific grant from funding agencies in the public,  
274 commercial, or not-for-profit sectors.

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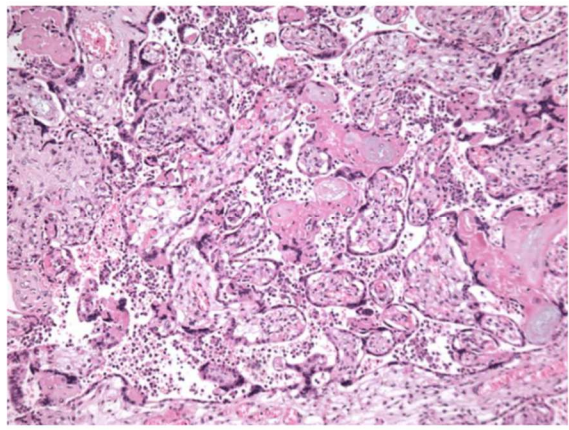
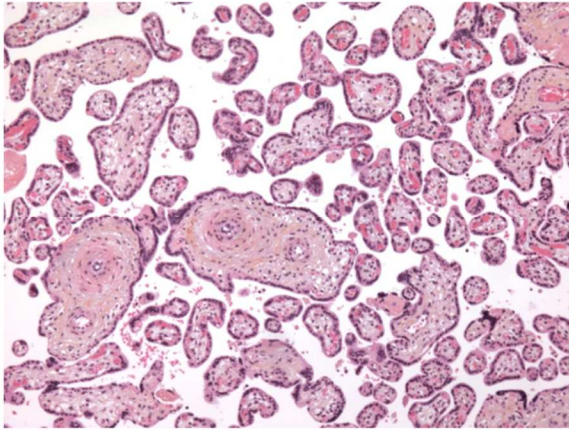
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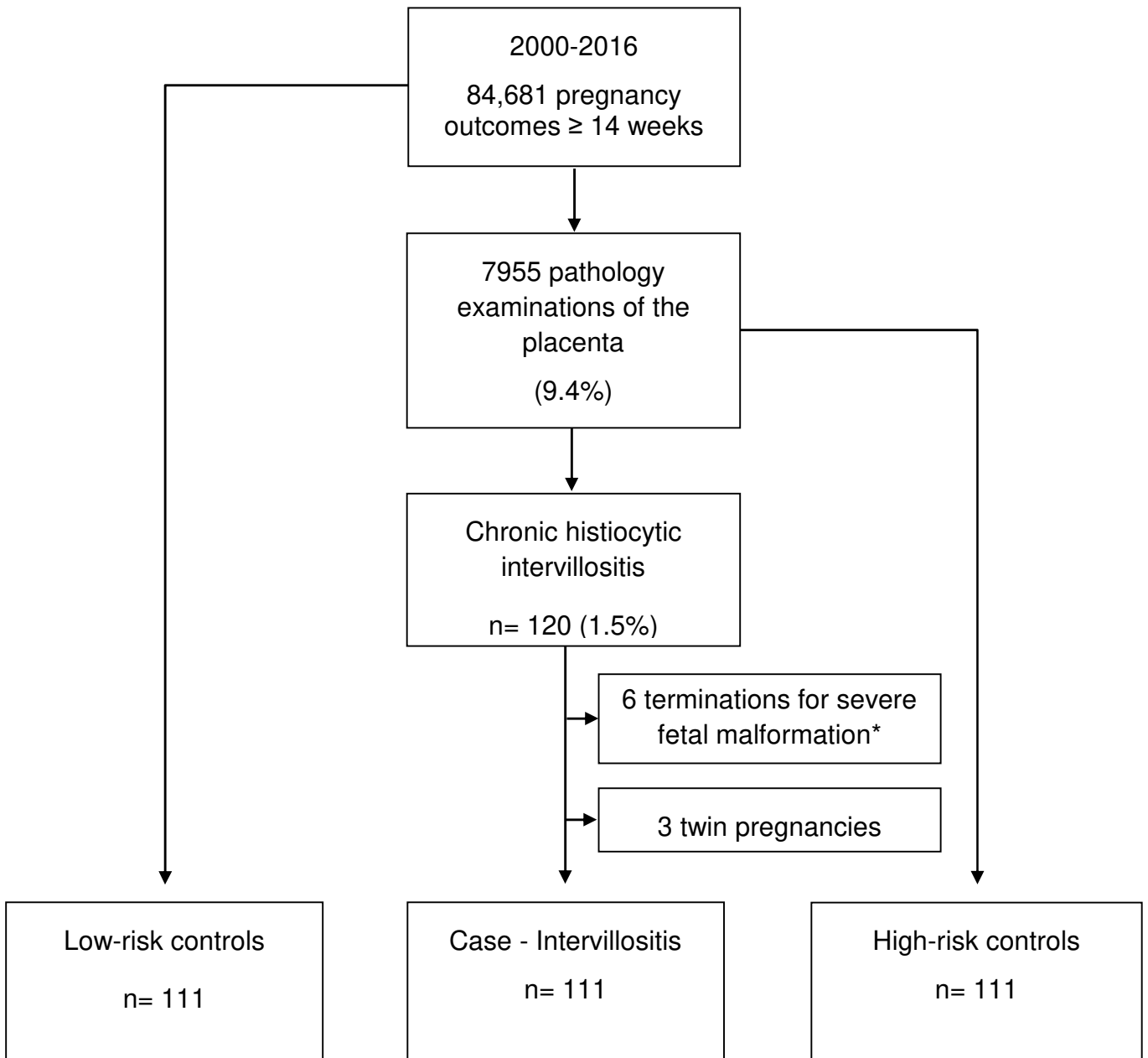


Table 1. Principal reason for placental examination in the different study groups <sup>a</sup>

	(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)	
Spontaneous preterm delivery (22-36 <sup>+6</sup> weeks)	3 (2.7)	-	20 (18.0)	<b>&lt;0.001</b>
Late miscarriage (14-21 <sup>+6</sup> weeks)	6 (5.4)	-	1 (0.9)	
Other	1 (0.9)	-	11 (9.9)	

<sup>a</sup> 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 at high risk n= 111	(1) vs (3) p
Maternal age (years)	30.8 ± 5.9	28.9 ± 5.5	<b>0.02</b>	28.7 ± 5.6	<b>0.01</b>
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]	<b>&lt;0.001</b>	1.6 [0-2]	<b>&lt;0.001</b>
History of early miscarriage <14 weeks	44 (39.6)	21 (19.3)	<b>&lt;0.001</b>	29 (26.1)	<b>0.03</b>
History of late miscarriage (14-21 <sup>+6</sup> )	6 (5.4)	0 (0.0)	<b>0.03</b>	2 (1.8)	0.28
History of in utero death	19 (17.1)	3 (2.7)	<b>&lt;0.001</b>	3 (2.7)	<b>&lt;0.001</b>
History of CHI	20 (18.0)	0 (0.0)	<b>&lt;0.001</b>	0 (0.0)	<b>&lt;0.001</b>

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	<b>0.02</b>
≥ 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	<b>&lt;0.001</b>	1.32 ± 0.69	<b>0.01</b>
≥ 2.5 MoM	10 (34.5)	0 (0.0)	<b>&lt;0.001</b>	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)	<b>&lt;0.001</b>	20 (18.0)	<b>0.01</b>
Abnormal karyotype	1 (2.7) <sup>a</sup>	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)	<b>0.01</b>	19 (17.1)	0.12
with HELLP syndrome	5 (5.3)	0 (0.0)	<b>0.02</b>	4 (3.8)	0.74
Estimated fetal weight <10 centile during pregnancy	73 (65.8)	6 (5.5)	<b>&lt;0.001</b>	57 (51.3)	<b>0.03</b>

Table 3. (continued)

Oligohydramnios on ultrasound	47 (42.3)	5 (4.7)	<b>&lt;0.001</b>	27 (26.2)	<b>0.01</b>
Abnormal uterine Doppler spectrum <sup>b</sup>	36/83 (43.4)	7/17 (36.8)	0.60	28/53 (52.8)	0.28
Abnormal umbilical Doppler spectrum <sup>c</sup>	33/81 (40.7)	2/40 (4.9)	<b>&lt;0.001</b>	20/77 (26.0)	<b>0.05</b>
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)	<b>&lt;0.001</b>	42 (37.8)	<b>0.02</b>
Last rate (IU/L)	625 ± 759	242 ± 201	0.05	191 ± 105	<b>0.002</b>
Gestational age at last assay (weeks)	28.6 ± 6.7	35.5 ± 4.6	<b>&lt;0.001</b>	30.1 ± 6.6	0.22
Rate > 600 IU/L	18 (30.0)	1 (4.8)	<b>0.01</b>	0 (0.0)	<b>&lt;0.001</b>

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

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 high risk n= 111	(1) vs (3) p	OR [95% CI]
Late miscarriage (14-21 <sup>+6</sup> )	6 (5.4)	0 (0.0)	<b>0.03</b>	Undefined	1 (0.9)	0.12	6.3 [0.73-141]
Termination of pregnancy <sup>a</sup>	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)	<b>&lt;0.001</b>	59.6 [8.5-1192]	13 (11.7)	<b>&lt;0.001</b>	4.1 [1.9 -8.7]
14-21 <sup>+6</sup>	17 (15.3)	0 (0.0)	<b>&lt;0.001</b>	Undefined	6 (5.4)	<b>0.015</b>	3.2 [1.1-9.4]
22-42	22 (19.8)	1 (0.9)	<b>&lt;0.001</b>	27.2 [3.4-550]	7 (6.3)	<b>0.003</b>	3.7 [1.4-10.0]
Gestational age at delivery <sup>b</sup>	33.6±4.7	39.4±2.6	<b>&lt;0.001</b>		35.1±5.0	<b>0.024</b>	
22-27 <sup>+6</sup> weeks	13 (14.7)	2 (1.8)			12 (11.5)		
28-36 <sup>+6</sup> weeks	50 (56.8)	6 (5.4)	<b>&lt;0.001</b>		45 (43.3)	<b>0.06</b>	
> 37 weeks	25 (28.4)	103 (92.8)			47 (45.2)		
Live birth ≥ 22 weeks	62 (55.9)	110 (99.1)	<b>&lt;0.001</b>	0.01 [0.0-0.08]	94 (84.7)	<b>&lt;0.001</b>	0.23 [0.11-0.45]
Preterm birth <sup>c</sup>	40 (64.5)	7 (6.4)	<b>&lt;0.001</b>	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)	<b>&lt;0.001</b>	29.1 [9.6-94.2]	39 (41.5)	0.05	2.0 [0.97-4.0]

Table 4. (continued)

Birth weight (grams) <sup>b</sup>	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 < 3 <sup>rd</sup> percentile ≥ 22 weeks <sup>b</sup>	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 <sup>b</sup>	-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	
Live births only <sup>c</sup>	-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 <sup>c</sup>	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) <sup>b</sup>	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]

<sup>a</sup> The 7 terminations were performed ≥ 22 weeks including 6 for severe fetal growth restriction <sup>b</sup> Births ≥ 22 weeks, live-born child or not <sup>c</sup> 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 < 3 <sup>rd</sup> percentile ≥ 22 weeks <sup>a</sup>	10/15 (66.7)	6/7 (85.7)	3/6 (50.0)	49/70 (70.0)	0.84
Birthweight expressed as z score <sup>a</sup>	- 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

<sup>a</sup> Births ≥ 22 weeks, live-born child or not