

ORIGINAL ARTICLE

Chronic histiocytic intervillitis: Outcome, associated diseases and treatment in a multicenter prospective study

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Abstract

Introduction: In this prospective multicenter study, we aimed to describe (1) the outcome of pregnancy in the case of previous chronic histiocytic intervillitis (CHI), (2) the immunological findings and associated diseases, (3) the treatments, and (4) the factors associated with pregnancy loss. **Methods:** We prospectively included all patients with a prior CHI with ongoing pregnancy between 2011 and 2013. **Results:** Twenty-four women (age 34 ± 5 years) were included in this study. An autoimmune disease was present in seven (29%) cases. Twenty-one prospective pregnancies were treated. The number of live births was more frequent comparatively to the previous obstetrical issues (16/24 versus 24/76; $p = 0.003$). Most of the pregnancies were treated (88%), whereas only 13% of previous pregnancies were treated ($p < 0.05$). No difference was found with respect to the pregnancy outcome in the different treatment regimens. In univariate analyses, a prior history of intrauterine death and intrauterine growth restriction and the presence of CHI in prospective placentas were associated with failure to have a live birth. **Discussion:** In this multicenter study, we show the frequency of the associated autoimmune diseases in CHI, as well as the presence of autoantibodies without characterized autoimmune disease. The number of live births increased from 32% to 67% in the treated pregnancies. Despite the treatment intervention, the risk of preterm delivery remained at 30%. Last, we show that the recurrence rate of an adverse pregnancy outcome persisted at 30% despite treatment intervention. **Conclusion:** CHI is associated with high recurrence rate and the combined regimen seems to be necessary, in particular, in the presence of previous intrauterine death.

Introduction

Chronic histiocytic intervillitis (CHI) is a rare placental lesion characterized by an intervillous infiltrate of maternal mononuclear inflammatory cells [1,2]. CHI is usually associated with unfavorable obstetrical outcomes, such as recurrent miscarriage, intrauterine growth restriction (IUGR), and intrauterine death, with a high risk of recurrence [3].

Several reports have previously analyzed the outcome of pregnancies with CHI in only retrospective studies, but

Keywords

Autoimmune disease, chronic histiocytic intervillitis, outcome, treatment

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some issues remain to be determined [4–11]. The pathogenesis of CHI could involve immunological dysregulation, but immunological screening and associated immunological disorders have not been adequately studied for CHI. Even if the recurrence rate of CHI seems to be high, prospective studies are lacking, and the factors associated with unfavorable outcomes remain to be determined. Moreover, although several reports describe CHI treatment, mostly with aspirin and steroids, the efficacy of each treatment intervention remains controversial, and studies comparing different treatment regimens in CHI are lacking, especially for the subsequent pregnancies in patients with a history of CHI [6,8,9].

In this prospective, multicenter study, we aimed to describe (1) the outcome of subsequent pregnancies in women with

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a previous CHI, (2) the immunological findings and associated diseases, (3) the efficacy of different treatment regimens, and (4) the factors associated with pregnancy loss.

Patients and methods

Patients

We prospectively included all patients with a previous CHI who had at least one pregnancy between 2011 and 2013. The diagnosis of CHI during a previous pregnancy was based on a histological evaluation of the placenta. CHI was defined by the presence of diffuse mononuclear cell infiltrates in the intervillous space in the absence of malaria and CMV infections. The histiocytic origin of the infiltrates was confirmed by testing for anti-CD68 antibodies if necessary. This study was approved by the local ethics committee (Comité de Protection des Personnes, Aulnay Ile de France X).

For each patient, data on the general patient characteristics, previous obstetrical history, parity, treatments during previous pregnancies, associated diseases, and previous placental examinations were collected when available.

For the subsequent pregnancies, the following data were collected: spontaneous abortion <10 weeks of gestation, maternal complications (thrombosis, preeclampsia, hemolysis, elevated liver enzymes, low platelets or HELLP syndrome, diabetes, and gravida hypertension), fetal complications (intrauterine deaths and IUGR), start date and characteristics of treatments, delivery, and term of delivery. For neonates, the birth weight, the presence of neonatal complications, and the number of intensive unit admissions were collected.

For each pregnancy, standard biological determinations including the CH50, C4, and C3 levels and immunological analyses were collected. Immunological parameters included the evaluation of antinuclear antibodies, anti-ENA (extractible nuclear antigens), anti-dsDNA, anti-phospholipid, anti-smooth muscle, anti-mitochondrial, ANCA, anti-liver-kidney and microsomal antibodies, antithyroglobulin and anti-TPO, as well as anti-gastric parietal cell and anti-transglutaminase antibodies (when available). Antinuclear antibodies were positive when the titer was >1/160. Anti-cardiolipins antibodies (ACL) and anti- β_2 -glycoprotein I (β_2 GPI) antibodies were determined using commercial enzyme-linked immunosorbent assays (Instrumentation Laboratory, Bedford, MA, and ThermoFisher Scientific, Waltham, MA, respectively). Lupus anticoagulant (LA) was detected using dilute Russell's viper Venom and the dilute activated partial thromboplastin time as screening tests. The cut-off values for the medium titer (99th percentile) were 20 UGPL for IgG and 20 UMPL for IgM ACL as well as 15 U/ml for the IgG and IgM anti- β_2 GPI antibodies. The following non-criteria anti-phospholipid antibodies were determined: IgG and IgM anti-phospholipid, IgG and IgM anti-phosphatidylethanolamine, IgG anti-annexin V, and IgG and IgM anti-prothrombin/phosphatidylserine (PS/PT) antibodies. Serologies for HIV 1-2, HCV, and HBV were negative for all included patients.

The placentas were analyzed for the following parameters: weight, the presence and type of macroscopic and microscopic lesions, and the presence of CHI and villitis. Because placental analyses of all previous pregnancies were not always

available, the placental findings of the pregnancies were compared with the available placental analysis of the most recent previous pregnancy for each case.

Statistical analysis

Quantitative data are expressed as the means and standard deviation according to their distribution, while qualitative data are expressed as numbers with the frequencies.

With 24 patients included in this study, the percentage of live births was estimated with a precision of approximately 20% and a two-sided risk of 5%. Fisher's exact test or χ^2 test was used to compare qualitative variables while the non-parametric Wilcoxon test was used for continuous variables, as appropriate.

To determine the factors associated with live births and term >37 weeks of gestation, the logistic univariate regressions included the following factors: the number of previous pregnancies (total, pathological, and normal), the number and type of previous pregnancy complications [spontaneous abortion <10 weeks of gestation, intrauterine death (between 10 and 20 weeks; >20 weeks of gestation), IUGR, and preeclampsia], the number of previous pregnancies with CHI, the prospective pregnancy complications, the associated histological placental characteristics of the previous pregnancies, the prospective pregnancy treatments (type and start time), the presence of auto-immune disease, the CH50-C4-C3 levels, and the presence of antinuclear antibodies and of conventional anti-phospholipid antibodies (LA, anti- β_2 GPI, ACL). Because the number of patients was limited, we did not perform multivariate analysis. Statistical analysis was performed using SAS (version 9.1) (SAS Inc., Cary, NC), and significance was defined as $p < 0.05$.

Results

Patient characteristics

From 2011 to 2013, 24 pregnant women with a previous history of CHI presented a subsequent pregnancy. The patient characteristics, previous obstetrical history, and pregnancy outcome are presented in Table 1. Sixteen pregnancies (67%) resulted in live-born births. During the 24 pregnancies, three were untreated and different treatment regimens were used in the 21 remaining pregnancies. The different treatments were aspirin in 20 cases (95%) (beginning term 7 ± 9 weeks of gestation), low-molecular weighted heparin (LMWH) in 14 cases (67%) (10 ± 6 weeks), prednisone in 15 cases (71%) at 12.6 ± 5 mg/day (7 ± 6 weeks), and hydroxychloroquine in six cases (29%). Aspirin or LMWH was used alone ($n = 4$), aspirin was associated with prednisone ($n = 6$), aspirin with prednisone and LMWH ($n = 5$), and aspirin, prednisone, LMWH and hydroxychloroquine all ($n = 6$).

Associated autoimmune disorders

An underlying autoimmune disease was present in seven cases, including APS ($n = 1$), Sjogren's syndrome ($n = 2$), systemic lupus erythematosus (SLE) with Sjogren's syndrome ($n = 1$), celiac disease ($n = 2$), and incomplete SLE (joint involvement, Raynaud phenomena, anti-nuclear antibodies, and anti-PS/PT associated with anti-phospholipid antibodies).

Table 1. Patients' characteristics and prospective pregnancy outcomes.

Characteristics	N = 24
Age (years)	34 ± 5
BMI (kg/m ²)	26 ± 7
Chronic arterial hypertension/mellitus diabetes	1 (4%)/0
Tobacco/alcohol use	3 (12.5%)/0
Ethnic origin: Caucasians	11 (46%)
Previous obstetrical history	N = 76 pregnancies
Normal pregnancies	12 (16%)
Spontaneous abortion <10 weeks of gestation	27 (35.5%)
Fetal death >10 weeks of gestation	25 (33%)
• Between 10 and 20 weeks of gestation	9 (12%)
• >20 weeks of gestation	16 (21%)
Live births	24 (32%)
Subsequent pregnancy	N = 24
Spontaneous pregnancy	24 (100%)
Spontaneous abortion <10 weeks of gestation	4 (16.6%)
Fetal death >10 weeks of gestation	4 (16.6%)
Live births	16 (67%)
Mothers complications: thrombosis/arterial hypertension	1 (4%)/2 (8%)
IUGR	3 (18%)
Preeclampsia	0
Preterm <37 weeks of gestation	5 (31%)
Term (live births only)	38 ± 1.6
Spontaneous delivery	5/16 (31%)
Birth weight/height/cranial perimeter (g/cm)	2943 ± 678/48 ± 1/34 ± 1
Birth weight <2500 g	3/16 (18%)

IUGR, intrauterine growth restriction; CHI, chronic histiocytic intervillitis; BMI, body mass index. All values are expressed as the means with the respective SD or numbers with frequencies.

Table 2. Patients' immunological findings (n = 20).

Immunological results	Values
CH50 (%)/C4 (mg/l)/C3 (mg/l)	107 ± 17/266 ± 57/1128 ± 177
Lupus anticoagulant	1 (5%)
Anti-cardiolipin IgG/IgM	1 (5%)/0
Anti-B2GPI IgG/M	0
Anti-phospholipid IgG/M	3 (27%)/0
Anti-phosphatidylethanolamine IgG/M	2 (18%)/0
Anti-annexine V/anti-prothrombin/ anti-phosphatidylserine	0
Anti-PS/PT	1 (9%)
Antinuclear antibodies	6 (30%)
Anti-dsDNA	0
Anti-SSA	3 (15%)
Anti-transglutaminase antibodies	2 (10%)
Anti-thyroid antibodies (anti-thyroglobulin and anti-TPO)/TSH (mU/L)	0/1.2 ± 0.2
Anti-mitochondrial antibodies	1 (5%)

Values are given as the numbers with frequencies.

The immunological results (n = 20) are shown in Table 2. Non-criteria APL were present in three cases, including anti-phosphatidylethanolamine IgG (n = 2) and anti-PS/PT associated with anti-phospholipid antibodies (n = 1), and these three cases were associated with clinical obstetrical APS manifestations of the Sapporo criteria [12,13]. Antinuclear antibodies were present in 6/20 cases, including Sjogren's syndrome (n = 3, anti-SSA antibodies), incomplete SLE (n = 1), and isolated antibodies (n = 2) with negative anti-ECT antibodies.

In mothers with autoimmune diseases, the number of live births was not significantly different from those who did not have autoimmune diseases.

Pregnancy outcome

The number of live births was significantly more frequent for subsequent pregnancies than previous obstetrical issues (16/24 [67%] versus 24/76 [32%]; *p* = 0.003). Almost all pregnancies were treated (88%), whereas only 13% of previous pregnancies with CHI were treated (*p* < 0.05). The treatments during the previous treated pregnancies (13%) were aspirin alone and associated with LMWH, and thus the use of prednisone and hydroxychloroquine was more frequent in subsequent pregnancies. No difference was found in the subsequent pregnancy outcome with different treatment regimens or preconception use. Nevertheless, the number of combined treatments was significantly correlated with the number of previous pathological events (*p* < 0.05). Thus, more combined treatments regimen were prescribed more frequently in patients with more previous pathological events, whereas patients without treatment or with monotherapy have less previous pathological events and mainly spontaneous abortion <10 weeks of gestation (Figure 1).

Placenta studies

The number of associated macroscopic and microscopic lesions in 24 pregnancies decreased in comparison with the placentas from the last previous pregnancies with CHI (Table 3). CHI was still present in 7/14 of the placentas from prospective pregnancies: in three pregnancies with live births, in two spontaneous <10-week abortions, and two intrauterine deaths. CHI was absent in the remaining seven pregnancies with live births (*p* = 0.07).

Risk factors of CHI recurrence

In univariate analysis, the presence and the number of previous intrauterine deaths >10 weeks (in particular between 10 and 20 weeks of gestation, but not >20 weeks), of previous IUGR and CHI on the subsequent placentas, were significantly associated with failure to have a live birth, whereas the type and start date of treatment, as well as the presence of other histological abnormalities did affect the pregnancy outcome. None of the analyzed factors were significantly associated with prematurity (<37 weeks of gestation).

Recurrence was observed in 8/24 prospective pregnancies (30%) (four had spontaneous loss <10 weeks and four had intrauterine deaths), with documented recurrent CHI in 4/4 of the available placental studies (two spontaneous loss <10 weeks and two intrauterine deaths).

Discussion

In this multicenter study, we studied, for the first time, the pregnancy outcome of patients with previous CHI with several specific issues. First, we show the frequency of the associated autoimmune diseases in CHI, as well as the presence of various autoantibodies. Second, the number of live births increased from 32% to 67% in the treated pregnancies. Despite the treatment intervention, the risk of

Figure 1. The treatment regimen in relation with previous obstetrical events.

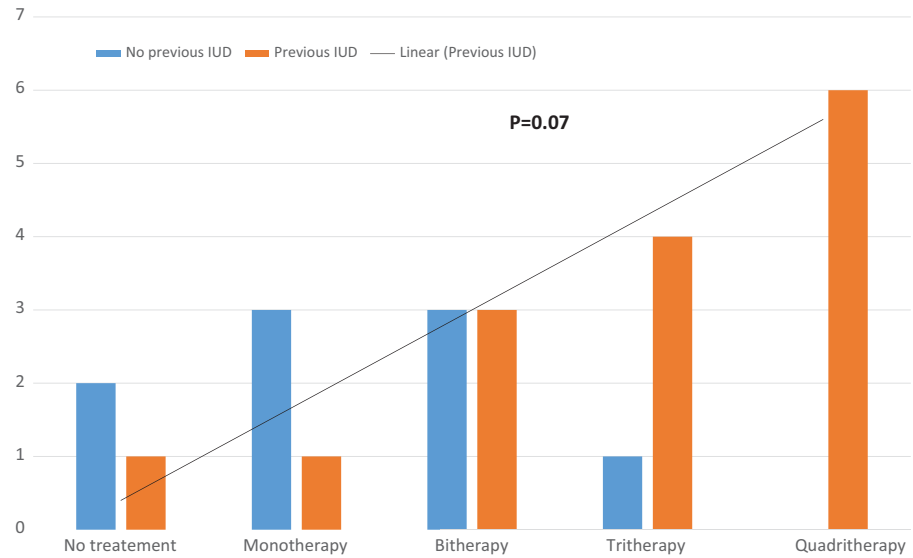


Table 3. Histological placental findings.

	Previous pregnancy placenta, N = 17	Prospective pregnancy placenta, N = 14
N treated	3 (18%)	12 (86%)*
Placenta weight	254 ± 156	413 ± 115
Pregnancy gestational age	27 ± 9	29 ± 12
Macroscopic lesions	12 (82%)	5 (36%)*
Vascular macroscopic lesions	6 (35%)	4 (29%)
Microscopic lesions	17 (100%)	9 (64%)*
Vascular microscopic lesions	7 (41%)	5 (36%)*
CHI	17 (100%)	7 (50%)*
Villitis	6 (35%)	1 (7%)

* $p < 0.05$.

preterm delivery remained at 30% in our case series. Even if the number of included patients does not allow for multivariate analysis, several parameters, such as the presence of previous IUGR and intrauterine deaths, but not spontaneous abortion < 10 weeks of gestation, could be associated with adverse outcomes in the consecutive pregnancies. More the number of previous pathological events was important, in particular the presence of intrauterine deaths, more treatment combinations were prescribed to obtain live births, as was the use of prednisone and hydroxychloroquine. Last, we show that the recurrence rate of an adverse pregnancy outcome persisted at 30% despite treatment intervention, as reflected by the persistence of placental CHI.

Previous limited retrospective case-series have shown various rates of IUGR (from 17% to 83%), intrauterine deaths (from 17% to 77%), and live births (from 32% to 83%) in mostly untreated pregnancies (Table 4). In our prospective study, with 88% of the pregnancies treated, the rates of adverse pregnancy outcome seemed to be lower with a higher number of live births (Table 4) [1–3,5–8,10,11,14]. Few retrospective studies have analyzed the recurrence rates of CHI, and the published studies have reported various rates (from 18% to 67%); the rate was estimated to be 30% in our prospective study. The persistence of histological CHI was not always associated with an adverse outcome in our study, even

if its absence correlated with live births. Few studies have described the use of a treatment intervention in CHI, which consisted mainly of aspirin, steroids or a combination of these two medications [3,6–9]. In a literature review of treated CHI, there was no observed proven benefit of treatment for obtaining a live birth, even though the number of included patients was low [9]. In this report, we evaluated the efficacy of a treatment intervention for CHI compared with previously untreated pregnancies, and the number of live births was significantly increased from 32% to 67% in the subsequent pregnancies. The rate of preterm births, which was as high as 74% in the largest CHI case-series [10], was 30% in our treated pregnancies. The comparison of different treatment regimens, including aspirin, low-molecular-weighted heparin, prednisone, and hydroxychloroquine (alone or in combination), failed to determine the best strategy to achieve live births, but the prednisone and hydroxychloroquine were used more frequently in patients with subsequent pregnancies. The prescription of more treatment combination in the case of patients with more aggressive disease could explain these discrepancies, as shown in patients with more previous adverse events. We describe, for the first time, the use of hydroxychloroquine in CHI with autoimmune diseases, which was associated with live birth in 4/6 cases. The absence of treatment guidelines, the presence of patients with previous history of treated CHI, of previously unrecognized CHI and patients with underlying AID could explain this treatment heterogeneity in our study. The presence of CHI has previously been shown in several patients with APS miscarriages, whereas CHI prevalence in spontaneous loss could be estimated at 9% [15,16].

Few autoimmune diseases, in particular SLE and autoimmune thyroiditis, have been described in association with CHI. The presence of autoimmune disorders was noted in 29% of our patients, as were several cases of possible seronegative APS, with the presence of non-criteria APL, especially the anti-phosphatidylethanolamine antibodies. Although the mechanism of the underlying CHI is not well established, CHI is usually considered an immunological disturbance that could be initiated by allo- or autoimmune

Table 4. Literature review and our case-series of CHI.

Author/year	Patients/ pregnancies	Miscarriage	IUGR	IUD/stillbirth	Live births	Recurrence	Live births in treated pregnancies
Labarrere 1987	6 19	4	5	1	14	2/7	NA
Jacques 1992	6 6	NA	NA	5	1	NA	0/2
Doss 1995	1 13	5	0	6	2	3	2/2
Boyd 2000	21 97	50	5/8	25	22	6/9	NA
Boog 2006	1 4	0	1	3	1	2	1/1
Rota 2006	25 27	3	21/27	15	9	NA	1/3
Parrant 2009	14 20	3	16	9	8	3/3	1/3
Marchaudon 2011	50 69	21	24	27	21	9/50	NA
Traeder 2010	4 8	3	4	2	3	NA	NA
Capuani 2012	12 16	4	10	5	7	NA	NA
Reus 2013	22 30	6		14	10	NA	NA
Our case series	24 24	4	3	4	16	7/14	14/21
Total	333	103/327 (31%)	84/200 (42%)	115/333 (35%)	114/333 (34%)	32/100 (32%)	19/32 (59%)

Values are given as the numbers with the frequencies. Recurrence is estimated as the number of persistent CHI cases according to the number of total available placental examinations.

triggers [17,18]. The expression of ICAM-1 by the syncytiotrophoblasts have been found to be particularly important in CHI. The maternal macrophages and lymphocytes T, whose number is increased in CHI, could release the proinflammatory cytokines which are able to induce the ICAM-1 expression [14,17]. Surprisingly, T-regulatory cells have been shown to be increased in decidua basalis and the intervillous space in patients with CHI, even a functional deficiency of this T subset remain to be determined in CHI [14]. Other mechanisms, as deregulated cell deaths, able to alarm the immune system, and implicated in preeclampsia, could also be impaired during the immune response in CHI [19]. Altogether, the dysregulation of placental immunoregulatory signals which could underline the presence of autoimmune diseases highlights the need to better determine the immunomodulation strategies in these patients.

A challenging issue is to determine the factors predictives of an adverse outcome in patients with a history of CHI. Several factors have been previously recognized, such as the CHI histological grade, elevated alkaline phosphatases of placental origin, or the presence of CHI in the trophoblastic antenatal biopsy [7,8,10]. In our study, these factors could not be assessed, and the characteristics of the previous obstetrical history and persistent histological CHI were the main factors associated with a recurrent, unfavorable outcome. Nevertheless, we are still lacking a biomarker that can predict the recurrence of CHI during consecutive pregnancies. Such a biomarker would help us better adapt the treatment strategy.

This study has several limitations. The number of included patients was low and prevented us from conducting a multivariate analysis to determine the factors that are independently associated with an adverse pregnancy outcome. The diversity of the treatment regimens limits definite

conclusions regarding the efficacy of each treatment intervention. A better pregnancy outcome could be related to the natural evolution and be influenced by the recurrence rate, even if the histological CHI was significantly less frequent in prospective pregnancies. The higher prevalence of autoimmune disorders could be explained by the design of the study, which included the participation of internal medicine specialists in most of the participating centers. The multi-center design and the absence of centralized placental analysis prevented CHI grading, whereas the CHI histological grade could be associated with an adverse pregnancy outcome.

Conclusion

CHI is associated with high recurrence rate and the treatment seems to be useful to avoid the adverse events. Even the better strategy remain to be determined, the combined regimen seem to be necessary, in particular, in the presence of previous intrauterine death.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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