Placenta 61 (2018) 80–88

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

Towards standardized criteria for diagnosing chronic intervillositis of unknown etiology: A systematic review

M. Bos [a, *], P.G.J. Nikkels [b], D. Cohen [a], J.W. Schoones [c], K.W.M. Bloemenkamp [d], J.A. Bruijn [a], H.J. Baelde [a], M.L.P. van der Hoorn [e], R.J. Turner [a]

[a] Department of Pathology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands
[b] Department of Pathology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
[c] Walaeus Medical Library, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands
[d] Department of Obstetrics, University Medical Center Utrecht, Wilhelmina Children's Hospital, Birth Centre, Lundlaan 6, 3584 EA Utrecht, The Netherlands
[e] Department of Obstetrics, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands

ARTICLE INFO

Article history:
Received 13 September 2017
Received in revised form
5 November 2017
Accepted 20 November 2017

Keywords:
Chronic intervillositis
Chronic intervillositis of unknown etiology
Fetal loss
Miscarriage
Intra uterine growth restriction
Small for gestational age

ABSTRACT

Chronic intervillositis of unknown etiology (CIUE) is a poorly understood, relatively rare condition characterized histologically by the intervillous infiltration of mononuclear cells in the placenta. Clinically, CIUE is associated with poor pregnancy outcome (e.g., impaired fetal growth, preterm birth, fetal death) and high risk of recurrence in subsequent pregnancies. Because CIUE is not defined consistently, it is essential to clearly define this condition. We therefore review the published definitions of CIUE. In addition, we provide an overview of the reviewed histopathological and maternal characteristics, obstetric features, and pregnancy outcomes. Medical publication databases were searched for articles published through February 2017. Eighteen studies were included in our systematic review. The sole inclusion criterion used in all studies was the presence of intervillous infiltrates. Overall, CIUE was characterized by adverse pregnancy outcome. Miscarriage occurred in 24% of cases, with approximately half of these miscarriages defined as late. Impaired growth was commonly observed, 32.4% of pregnancies reached term, and the live birth rate was 54.9%. The high recurrence rate (25.1%) of the intervillous infiltrates in subsequent pregnancies underscores the clinical relevance of CIUE, the need for increased awareness among pathologists and clinicians, and the need for further research. Criteria for the diagnosis of CIUE are proposed and a Delphi study could be used to resolve any controversy regarding these criteria. Future studies should be designed to characterize the full clinical spectrum of CIUE.

Contents

ABBREVIATIONS: CIUE, chronic intervillositis of unknown etiology.

* Corresponding author. Leiden University Medical Center, Department of Pathology, L1 Q PO Box 9600, P0-107 2300 RC Leiden, The Netherlands.
E-mail address: m.bos@lumc.nl (M. Bos).

https://doi.org/10.1016/j.placenta.2017.11.012

1. Introduction

Chronic intervillositis of unknown etiology (CIUE) is a poorly understood, relatively rare condition first described in 1987 by Labarrere and Mullen as massive chronic intervillositis. They defined massive chronic intervillositis as a histopathological finding characterized by the intervillous infiltration of mononuclear cells in the placenta, fibrin deposits and trophoblast necrosis [1]. CIUE appears to be associated with poor perinatal outcome, including miscarriage, reduced fetal growth, and fetal death [2,3]. In addition, CIUE has a 4–100% chance of recurrence in a subsequent pregnancy [2–6]. The incidence of CIUE in the second and third trimester is 6 out of 10,000 pregnancies, and CIUE-related miscarriage occurs in 44 out of 1000 pregnancies in which the fetus has a normal karyotype [4].

Nomenclature

In this review is referred to a condition that encompasses the presence of chronic intervillositis accompanied by pregnancy complications, a high recurrence risk, and the absence of a known (infectious) cause. Since these chronic intervillous infiltrates were first described as massive chronic intervillositis by Labarrere and Mullen, a variety of terms have been used to describe this condition, including *"chronic intervillositis of unknown etiology", "chronic intervillositis", "chronic histiocytic intervillositis of unknown etiology", "chronic histiocytic intervillositis", "massive histiocytic chronic intervillositis", "massive perivillous histiocytosis", "intervillitis", and "massive chronic intervillositis"* [8]. It is important to distinguish between chronic intervillositis referring to a histologic placenta lesion irrespective of the cause, and the specific condition we define. The term "chronic intervillositis of unknown etiology (CIUE)" should be used in further research on the condition we define in this systematic review.

Immunological and/or coagulation disturbances may play a role in the pathophysiology of CIUE. For example, the occurrence of intervillous infiltrates with focal villitis [2,5] and the presence of C4d deposits in CIUE are indicative of an immunological disturbance [7]. In addition, increased placental expression of intercellular adhesion molecule-1 [8] and the presence of CIUE-specific cell infiltrates [9] suggest an immunopathological component. Moreover, Reus et al. recently suggested that the pathophysiology of CIUE might be based on a HLA mismatch between the "donor" (fetal-paternal antigens) and the "recipient" (the mother); this suggestion was based on observations of mixed lymphocyte reactions and the prevalence of cytotoxic T lymphocyte precursors cells [10]. Furthermore, the presence of CIUE in cases with neonatal alloimmune thrombocytopenia, which is caused by maternal antibodies against paternally derived human platelet antigens, may suggest a process comparable to chronic rejection [11,12]. The presence of perivillous fibrin deposits in CIUE suggest coagulative disturbances, this likely is due to an immune-mediated process [4,13]. Interestingly, chronic intervillositis is also observed in the placentas of women with malaria and/or acute cytomegalovirus infection [14,15]. Although reduced fetal growth and preterm birth are also observed in pregnancies complicated by malaria, perinatal mortality is not frequently observed in these pregnancies [14]. The co-occurrence of chronic intervillositis and malaria has given rise to the hypothesis that an underlying, not yet identified, infection may be associated with CIUE.

Given that CIUE is associated with a high risk of recurrence and with adverse pregnancy outcome [2–6], prevention is the best approach. A few studies reported positive effects of treatment with aspirin, heparin, prednisolone, and/or corticosteroids in various dosages and combinations [2–4,16,17]. A meta-analysis by Contro et al. revealed that the reported live birth rate does not significantly improve with treatment [5]. However, more recent studies suggest a different combination therapy for CIUE, which was beneficial in few cases [18,19]. This combination treatment was not reviewed in the meta-analysis [5]. Extensive national or international studies including as many patients as possible are needed to elucidate the etiology of CIUE and to investigate therapeutic approaches.

Since different terms are used over the time to describe CIUE [8], it is likely that different definitions, inclusion criteria and exclusion criteria are used in various studies. Therefore, developing a clear definition of CIUE is an essential first step towards comparable study results and understanding the etiology of CIUE.

Our primary objective is to review the published definitions of CIUE, as well as the inclusion and/or exclusion criteria used in all studies regarding CIUE published from 1987 through February 2017. In addition, we provide an overview of the investigated histopathological parameters and immunological characteristics of the cellular infiltrates, and we review the clinical features, obstetric characteristics, and outcomes in the published cases. Based on

these results, we propose standardized criteria for diagnosing CIUE.

2. Methods

2.1. Search methods

The following databases were searched for articles regarding CIUE published from 1987 through February 2017: PubMed, Embase, Web of Science, Emcare, Academic Search Premier, ScienceDirect, Wiley-Blackwell, LLW, Highwire, and Google Scholar. Each database was searched using the following terms: *"massive chronic intervillositis", "chronic histiocytic intervillositis", "intervillositis", "perivillous histiocytosis"*, and *"intervillites"*. The literature search was performed by authors MB and JS. Complete details regarding the search strategy details are available in Appendix A.

2.2. Selection of studies

Potentially relevant studies were reviewed independently by authors MB and RT by scanning the article's title and abstract. All peer-reviewed publications regarding histologically confirmed cases of CIUE were included. We excluded non-observational studies, reports of an intervillous infiltrate due to documented infection, reports of other forms of villitis, case reports, and studies with no full text available. Any disagreement regarding including a study was resolved by consensus between authors MB and RT. The references were checked in the included studies, and citation tracking was performed.

2.3. Patient characteristics

Maternal age and gestational age were obtained from the patient data provided in each study and are reported as the mean, standard deviation, and range. Gravidity and parity were also obtained and were reported as median and range. In the event that data were not published per patient, we used the reported outcomes.

2.4. Pregnancy outcome

We collected the following data: the number of early and/or late miscarriage, growth restriction, preterm births, stillbirths, perinatal mortality, and the recurrence of CIUE in subsequent pregnancies. Miscarriage was defined as the spontaneous loss of pregnancy within the first 22 weeks of gestation [20]. Early and late miscarriages were defined as miscarriage that occurred at $\leq$12 weeks of gestation and 12–22 weeks of gestation, respectively. Intrauterine growth restriction was defined as an estimated fetal weight in the bottom 10th percentile for gestational age, and small for gestational age was defined as a birth weight in the bottom 10th percentile for the corresponding gestational age [21]. One study in a Hispanic population did not determine growth based on gestational age; we therefore determined these data using the appropriate reference curves for this population [22]. A term pregnancy was defined as birth $\geq$37 weeks, and preterm birth was defined as birth <37 weeks of gestation. In approximately 50% of early miscarriages, the fetus has a chromosomal abnormality [23]. However, cases of CIUE in a study group of early miscarriages have been reported to be karyotypically normal [24]. Maternal factors, such as coagulation abnormalities, are more predominant in late miscarriages [25]. Since both, early and late miscarriages, might have a different etiology, also in the context of CIUE, the proportions of term births were calculated with and without early miscarriages [26]. Worldwide, the definition used for stillbirth varies [27]. For our purposes, stillbirth was defined as pregnancy loss after 22 weeks of gestation [20]. A stillbirth event at term was considered as a pregnancy that reached term. Perinatal mortality refers to both stillbirths and neonatal deaths within the first postnatal week. We defined pregnancies resulting in a living child as the total number of pregnancies with gestational age $\geq$12 weeks minus the number of pregnancies that resulted in late miscarriage, stillbirth, or perinatal death. Cases with missing data were excluded separately for each outcome.

3. Results

3.1. Selected studies

Our literature search revealed 361 unique publications. Fig. 1 shows a flowchart of the inclusion and exclusion of these publications. First, 312 publications were excluded based on the title and/or abstract. Thirty-one of the remaining 49 publications were excluded for the following reasons: 16 were meeting abstracts, 13 were case reports that included fewer than three cases, and the full text was not available for one publication. Furthermore, one additional publication [28] was excluded because these cases were already included in two other publications [29,30]. Reference checking and citation tracking did not yield any new publications. Thus, a total of 18 publications met our criteria and were included in our systematic review [1–3,6–10,16–18,29–35]. These 18 publications reported a total of 291 women, including 350 pregnancies with either an intervillous infiltrate in the placenta diagnosed as CIUE or comparable lesions that were given a different name, e.g. massive chronic intervillositis, chronic intervillositis, chronic histiocytic intervillositis, chronic intervillitis or chronic histiocytic intervillositis of unknown etiology. The publications included in this review are summarized in Table 1.

3.2. Diagnostic criteria for CIUE

The inclusion and exclusion criteria for the collection of cases in the included studies are summarized in Table 2. Some groups did not clearly state their inclusion and/or exclusion criteria for selecting cases.

3.2.1. Inclusion criteria for the selection of cases

The only inclusion criterion used in all 18 studies was the presence of an infiltrate in the intervillous space. In 67% of the studies (12 publications) CIUE was defined explicitly as the presence of mononuclear cells in the intervillous space [1,2,6,7,9,10,16–18,31,33–35]. Nine groups (50%) mentioned that the infiltrate should contain histiocytes [3,6–8,18,29,31,32,34,35].

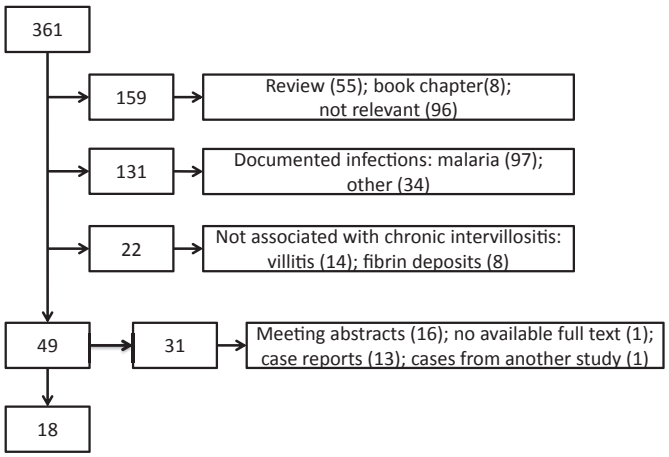

Fig. 1. Flowchart of the selection of publications included in this systematic review.

Table 1
Publications included in this systematic review.

	Study design	Term for intervillous infiltrates	Number of pregnancies with intervillous infiltrates	Number of women with intervillous infiltrates	Number of control pregnancies	Number of control patients	Type of controls	Total	Comment
Labarrere and Mullen, 1987 [1].	Re CC	Massive chronic intervillositis	6	6	12	12	Chronic villitis (12)	**18**	
Jacques and Qureshi, 1993 [16].	Re CS	Chronic intervillositis	6	6				**6**	
Boyd and Redline, 2000 [3].	Re CS	Chronic histiocytic intervillositis	31	21				**45**	
Rota et al., 2006 [17].	Re CS	Chronic intervillitis	28	25				**28**	
Parant et al., 2009 [2].	Re CS	Chronic intervillositis of unknown etiology	20	14				**20**	
Traeder et al., 2010 [29].	Re CS	Chronic histiocytic intervillositis	4	4				**4**	
Marchaudon et al., 2011 [31].	Re CS	Chronic histiocytic intervillositis of unknown etiology	69	50				**69**	
Heller, 2012 [32].	Re CC	Chronic histiocytic intervillositis	9	8	11	11	second-trimester cases with chromosomal abnormalities or multiple severe anomalies (11)	**20**	
Capuani et al., 2013 [9].	Re CS	Chronic histiocytic intervillositis of unknown etiology	20	16				**20**	
Freitag et al., 2013 [30].	Re CC	Chronic histiocytic intervillositis	2	2	11	11	Villitis of unknown etiology (4), normal placenta (7)	**16**	case 1, 3 and 4 from Traeder et al. (2010)
Reus et al., 2013 [10].	Re CS	Chronic histiocytic intervillositis	27	22				**30**	3 cases without an intervillous infiltrate
Labarrere et al., 2014 [8].	Re CC	Massive chronic intervillositis	7	7	14	14	villitis (7), without villitis or massive chronic intervillositis (7)	**21**	
Bendon et al., 2015 [7].	Re CC	Chronic intervillositis	32	28	32	31	Placentas of complicated and uncomplicated pregnancies with villitis of varying degrees.	**64**	We defined cases as placentas with massive chronic intervillositis (18) as well as placentas with few intervillous monocytes (14).
Labarrere et al., 2015 [33].	Re CC	Massive chronic intervillositis	17	17	34	34	Chronic villitis of unknown etiology (17), without chronic villitis of unknown etiology or massive chronic intervillositis (17)	**51**	
Mekinian et al., 2015 [18].	Pr CS	Chronic histiocytic intervillositis	24	24				**24**	
Revaux et al., 2015 [34].	Re CS	Chronic intervillositis	18	12				**38**	
Nowak C et al., 2016 [6].	Re CC	Chronic intervillositis of unknown etiology	24	23	154	143	Villitis of unknown etiology (78), villitis and intervillositis (76)	**178**	
Sabra et al., 2016 [35].	Re CS	Chronic histiocytic intervillositis	6	6				**6**	
			350	291					

18 studies were included in this systematic review. One study had a prospective study design. These studies describe 350 pregnancies with CIUE in 291 women. Several control groups were used in case-control studies. Data per patient were provided in eight studies. Abbreviations; Re, Retrospective; CC, Case-control study; CS, Case series; Pr, Prospective.

Table 2
Inclusion and exclusion criteria used for the diagnosis of CIUE.

	Labarrere and Mullen, 1987 [1].	Jacques and Qureshi, 1993 [16].	Boyd and Redline, 2000 [3].	Rota et al., 2006 [17].	Parant et al., 2009 [2].	Traeder et al., 2010 [29].	Marchaudon et al., 2011 [31].	Heller, 2012 [32].	Capuani et al., 2013 [9].	Freitag et al., 2013 [30].	Reus et al., 2013 [10].	Labarrere et al., 2014 [8].	Bendon et al., 2015 [7].	Labarrere et al., 2015 [33].	Mekinian et al., 2015 [18].	Revaux et al., 2015 [34].	Nowak C et al., 2016 [6]	Sabra et al., 2016 [35],.	
Inclusion criteria																			%
Intervillositis/ infiltrate in intervillous space	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Mononuclear infiltrate	+	+		+	+		+		+		+			+	+	+	+	+	67
Histiocytic monomorphic infiltrate			+			+	+	+				+			+	+	+	+	50
Infiltrate is massive/wide spread/diffuse	+		+							+		+		+	+	+			39
Fibrin deposits	+	+			+				+										22
Trophoblastic necrosis	+	+		+															17
Maternal origin of infiltrate											+					+		+	17
Exclusion criteria																			
Signs of infection	+			+	+				+	+		+		+	+	+	+	+	61
Villitis		+	+			+			+				+						28
Chorioamnionitis				+								+		+					17
Cytomegalovirus infection					+					+					+				17
The presence of "other obvious placental lesions"				+	+		+												17
Malaria															+			+	11
Polymorphic infiltrate			+			+													11
Infiltration/ destruction of placental tissue										+									6
Lymphocytic vasculitis				+															6
Congenital malformations																		+	6

Several inclusion criteria and exclusion criteria were used for the selection of patients. "+" in the table indicates that the study used this particular inclusion criterion or exclusion criterion. The only uniform inclusion criterion used was the presence of an intervillous infiltrate (100%). Most of the studies excluded pregnancies with signs of infections (61%).

Seven groups (39%) stated that only patients with a massive, diffuse, or widespread infiltrate in the intervillous space should be included [1,3,8,18,30,33,34]. Four and three groups used the presence of fibrin deposits and trophoblastic necrosis, respectively, as an inclusion criterion [1,2,9,16,17]. Finally, three groups stated that the infiltrate should be maternal in origin to be defined as CIUE [10,34,35].

3.2.2. Exclusion criteria for the selection of cases

Eleven groups (61%) specifically excluded patients with an infectious cause of CIUE [1,2,6,8,9,17,18,30,33,34]; four groups excluded patients with malaria or cytomegalovirus infection [2,18,30,35], three groups excluded patients with chorioamnionitis [8,17,33], and four groups excluded patients with other infectious diseases [1,6,9,34]. The largest discrepancy with respect to exclusion criteria was regarding the co-occurrence of chronic villitis with intervillositis; five groups excluded cases with chronic villitis [3,7,9,16,29], whereas one group explicitly stated that they included only cases with focal chronic villitis [2]. Marchaudon et al. reported that they excluded cases with intervillositis associated with other placental lesions [31].

3.3. Histopathological findings

Supplemental Tables 1 and 2 provide an overview of the histological findings and the composition of the cell infiltrates. One group found fibrin deposits in 18% of cases [17]; another group found fibrin deposits in 100% of cases [1]. Four groups used the presence of perivillous fibrin deposits as an inclusion criterion [1,2,9,16]; in contrast, groups that also mentioned the presence of fibrin deposits did not use this as an inclusion criterion [3,17,29,30]. The presence of fibrin was reported in different grades from low to diffuse [3,16,31]. Trophoblast necrosis and erosion were noted by Capuani et al. [9], and Labarrere et al. reported a prevalence of 100% in their original paper on massive chronic intervillositis [1]. The co-occurrence of villitis was observed in 25–76% of cases with CIUE [1,2,6,17,18,29,33]; however, the presence of villitis was also used as an exclusion criterion by six groups [2,3,7,9,16,29]. Two groups studied combined lesions with CIUE and villitis [6,7].

Five groups extensively studied the composition of the intervillous infiltrates [3,9,29,30,33]. The majority of cells (approximately 80%) were positive for CD68; moreover, Boyd et al. [3] found that approximately 30–40% of these CD68 $^{+}$ cells expressed MRP14. The marker MRP14 is also known as S100A9 [36], this marker is expressed by an activated immature monocyte/macrophage subset [37]. T cells (5–24%) and subtypes of T cells were also observed in the infiltrate, including ($CD8^{+}$) cytotoxic T cells (7.7–17.1% of cells), ($CD4^{+}$) T helper cells (5.1–14.4% of cells) [9,30,33], and regulatory T cells (approximately 5% of cells) [9]. Finally, one group reported that 4% of the cells in the infiltrate were B cells (see Supplemental Table 2) [9].

3.4. Maternal characteristics and obstetrical features

Eight of the publications reported the maternal characteristics, obstetrical features, and pregnancy outcomes per patient [1,2,7,9,16,29,30,35]. The maternal characteristics and obstetrical features varied widely among the studies (Table 3). Maternal age ranged from 18 years to 45 years, gravidity ranged from 1 to 11, and parity ranged from 0 to 8. The presence of CIUE was reported in placenta samples from all three trimesters. Several conditions and factors appeared to be associated with CIUE, including autoimmune disease, preeclampsia, assisted reproduction, and smoking (Supplemental Table 3) [3,8,10,16–18,29–31,33,34].

3.5. Pregnancy outcome

An overview of the documented pregnancy outcomes in patients

Table 3
Maternal characteristics and obstetrical features.

	Study provided data per patient	Mean maternal age, years (SD, years) [range, years]	Gravidity, median [range]	Parity, median [range]	Mean gestational age, days (SD, days) [range, days]
Labarrere and Mullen, 1987 [1].	+	30.5 (7.4) [21–42]	3.5 [1–5]	2 [1–5]	265 (14) [238–280]
Jacques and Qureshi, 1993 [16].	+	29.0 (4.6) [23–37]	3.5 [3–11]	1 [1–7]	191 (41) [140–266]
Boyd and Redline, 2000 [3].		29.8 (6.2) [20–43]	5 [1–9]		
Rota et al., 2006 [17].		30.1			
Parant et al., 2009 [2].	+	30 [24–39]	2.5 [1–10]	1 [0–6]	199 (65) [56–284]
Traeder et al., 2010 [29].	+	34.0 (4.2) [30–40]	1.5 [1–4]	1 [1–2]	218 (22) [189–249]
Marchaudon et al., 2011 [31].		31.2 (6.1) [16–43]			
Heller, 2012 [32].					
Capuani et al., 2013 [9].	+	30 (5.4)	3 [1–9]	0 [0–4]	188 (54) [77–273]
Freitag et al., 2013 [30].	+	[25–35]	[1–3]	[0–1]	[134–225]
Reus et al., 2013 [10].		31.8 (4.9) [22–45]	*mean (SD)*, 4.5 (3.1) [1–13]	*mean (SD)*, 2.3 (1.9) [0–8]	181 (72) [56–283]
Labarrere et al., 2014 [8].		*median*, 28 [21–42]	1 [0–4]	1 [0–4]	*median*, 266 [238–280]
Bendon et al., 2015 [7].	+		2.5 [1–11]		224 (50) [91–280]
Labarrere et al., 2015 [33].		*median*, 29 [18–42]	2 [1–6]	1 [0–4]	*median*, 266 [238–287]
Mekinian et al., 2015 [18].		34 (5)			
Revaux et al., 2015 [34].		*median*, 30 [22–40]			
Nowak C et al., 2016 [6].					
Sabra et al., 2016 [35].	+	34.8 (2.4) [32–39]	3 [2–6]	1 [0–1]	94 (62) [56–231]

The maternal characteristics of the included patients with an intervillous infiltrate and the obstetrical features of pregnancies complicated with CIUE varied widely among the studies. Two publications did not provide information regarding maternal characteristics. Abbreviations; SD, standard deviation.

with CIUE is provided in Supplemental Table 4. The overall incidence rates of each pregnancy outcome are shown in Table 4. Miscarriage was reported in 62 out of 256 (24.2%) pregnancies. This might be underestimated, as some groups included only pregnancies that resulted in a live birth [8,33]. Approximately 50% of miscarriages were late miscarriages (24 out of 52); in seven publications the majority of documented miscarriages were late miscarriages [2,6,7,9,16,30,32]. However, in two studies with a relatively high incidence of miscarriage, 70–82% of documented miscarriages were early miscarriages [3,31]. Impaired fetal growth was reported for nearly 65% of pregnancies. Specifically, 63 out of 88 fetuses had intrauterine growth restriction, and 40 out of 66 fetuses were small for their gestational age. The number of fetuses with impaired growth was slightly underestimated, as some groups defined impaired fetal growth as either an estimated fetal weight or birth weight in the bottom 3rd percentile of reference curves [6,31]. Only 59 out of 182 pregnancies (32.4%), which provided sufficient information on gestational age at birth, resulted in a term birth; this percentage increased slightly to 38.1% when early miscarriages were excluded. Fifty-five out of 190 documented pregnancies ended in stillbirth, and six neonatal deaths were documented [16]. Among the pregnancies with CIUE, 135 resulted in live-born infants (54.9%); this percentage increased to 59.4% when early miscarriages were excluded. The rate of recurrence among 199 women was 25.1% and ranged from 4.2% to 100%. One prospective study reported a recurrence rate of 33.3% among 24 women with CIUE [18].

4. Discussion

Our objective was to investigate the definitions, inclusion criteria, and exclusion criteria in studies regarding CIUE published since 1987. In addition, we provided an overview of the histological findings, maternal characteristics, obstetric features, and reported outcome of cases in the included studies. We found that studies regarding CIUE use different inclusion criteria and exclusion criteria for selecting cases with CIUE, or they used different definitions. Indeed, the only criterion used by all groups was the presence of an intervillous infiltrate in the placenta. Despite this wide variation among publications, all publications underline that CIUE is a serious condition characterized by adverse fetal outcome, including high rates of miscarriage, impaired growth, reduced term births, and a reduced live birth rate. In addition, the relatively high rate of recurrence (25.1% of patients) underscores the high clinical relevance of CIUE.

4.1. Strengths and limitations of this study

This study provides an accurate overview of publications describing the lesion CIUE. Furthermore, this review is the first step towards standardized criteria for diagnosing CIUE. Limitations of this study are the limited number of included patients and incomplete patient characteristics and obstetric characteristics, caused by the study design and reporting of included studies. For instance, some groups provided limited information regarding pregnancy outcome, used different criteria for pregnancy outcome, or reported the outcome of pregnancies with an intervillous infiltrate together with pregnancies without CIUE.

4.2. Limitations of the included studies

We found that the definitions used differed among publications; patient characteristics, histopathological findings, and pregnancy outcomes differed between studies, giving rise to the question whether CIUE is a self-contained entity.

With one exception [18], all the studies included in our review were retrospective studies. A retrospective study may favor the selection of patients with a severe and/or suspicious case history, thereby leading to selection bias. Furthermore, most of these cases were selected based on a previous diagnosis by a pathologist. Pathologists who do not specialize in examining placentas can experience difficulties in properly recognizing the lesion and therefore tend to diagnose the more severe cases [32]. On the other hand, pathologists who are familiar with CIUE may diagnose less suspicious cases. Kramer et al. reported high levels of both intra-observer and inter-observer agreement with respect to the histological features of acute placental inflammation [38]; however, such results can be generalized only to experienced placental pathologists [38]. Moreover, a diagnosis of CIUE is based on a process of elimination, most groups attempted to exclude an underlying infection. However, due to the retrospective study design, adequate patient materials (e.g., blood samples, frozen placental specimens, etc.) may not be available. This may lead to incorrectly diagnosing a case as well.

On the other hand, several groups reported a substantial risk of recurrence of CIUE after a reported lesion [3,7,9,18], and the outcome in patients with CIUE is generally less favorable compared with patients with placentas without any lesions, with villitis of unknown etiology, or with a combined lesion of villitis and intervillositis [1,6]. The recurrence of the infiltrates and adverse outcomes in patients with CIUE is in favor of CIUE being a self-contained entity. Furthermore, there appears to be an association between CIUE and autoimmune disease and it is striking that ten of the 18 publications mentioned that some of the included patients had preeclampsia (see Supplemental Table 3). Preeclampsia is a pregnancy-related syndrome characterized by impaired placental function, immune-dysregulation and subsequent maternal endothelial dysfunction [39]. These associations might provide some insights in a possible immunological etiology of CIUE. However, due to case selection, it is not possible to draw definitive conclusions. To determine whether CIUE is truly a self-contained entity and to reveal the etiology of CIUE, the presence of selection bias should be resolved in further studies and prospective studies should be performed.

Table 4
Summary of pregnancy outcomes.

	Miscarriage	Late miscarriage	IUGR	SGA	Term births	Pregnancies reaching term after 12 weeks of gestation	Stillbirth	Neonatal mortality	Live birth	Pregnancies resulting in a living child	Recurrence
Number of studies	15	7	7	7	11	11	13	2	13	11	10
Total number of pregnancies or patients	256	52	88	66	182	155	190	9	246	180	199
Number of pregnancies or patients with outcome	62	24	63	40	59	59	55	6	135	107	50
%	24.2	46.2	71.6	60.6	32.4	38.1	28.9	60.0	54.9	59.4	25.1

Number of studies represents the number of publications that reported the respective outcome; number of pregnancies or patients represents the number of patients included in those studies; number of pregnancies or patients with outcome represents the number of patients with the indicated outcome; % represents the of number of pregnancies or patients with the indicated outcome divided by the number of pregnancies or patients, expressed as a percentage. Abbreviations; IUGR, intrauterine growth restriction; SGA, small for gestational age.

4.3. Towards standardized criteria for the diagnosis of chronic intervillositis of unknown etiology

Based on our thorough analysis of articles on CIUE published from 1987 through February 2017, we propose standardized criteria for diagnosing CIUE.

Criteria for the diagnosis of chronic intervillositis of unknown etiology

Inclusion criteria

Criterion I: An infiltrate is present in the intervillous space.

Criterion II: Approximately 80% of the mononuclear-cells in the intervillous space are CD68-positive cells.

Criterion III: The intervillous space should be occupied by an infiltrate for 5% or more.

Exclusion criterion

Criterion IV: Cases with clinical or histopathological signs of infection should be excluded.

4.3.1. Characteristics of the intervillous infiltrates

The most important diagnostic criterion is the presence of an intervillous infiltrate containing predominantly mononuclear cells (Criterion I). Several groups suggested that these mononuclear cells in the intervillous space have a histiocytic phenotype [3,9,13,18,29–32,35]. The presence of histiocytes in the intervillous space can be confirmed with immunohistochemistry [32]. In five publications is suggested that approximately 80% of the cells in the intervillous infiltrates should be CD68+-cells (Supplemental Table 2) [3,9,29,30,33] (Criterion II), and the number of CD68+-cells in the intervillous space should be four-times higher than in normal placentas [32]. 5% or more of the placental intervillous space should be occupied by intervillous infiltrates [29] (Criterion III). The intervillous infiltrates should be present in at least two out of three full-thickness sections of macroscopic normal-appearing placenta parenchyma in third trimester placentas [40]. The required number of sections might not be available in first and second trimester samples, in these cases at least 5% or more of the placental invervillous space of the sampled specimen should contain intervillous infiltrates. The presence of a widespread infiltrate was used as an inclusion criterion in seven studies in our review and the severity of the infiltrate may be correlated with pregnancy outcome [2]. Severe intrauterine growth restriction and intrauterine fetal death were observed in cases with a severe infiltrate, and the perinatal prognosis was better in cases with a moderate infiltrate [2]. However, it is also reported that the intervillous infiltrate is less severe in cases complicated with intrauterine fetal death [31]. The severity of the infiltrate in relation to clinical outcomes is an interesting topic for more in-depth research. In three studies is suggested that the intervillous infiltrate should be of maternal origin [10,34,35], and this was confirmed in one study [29]. The maternal origin of the infiltrate is plausible, based on its location, but it is trivial for diagnosis criteria.

4.3.2. Co-occurring histopathological findings

The co-occurrence of different histopathological findings is not consistent in reported placentas with CIUE. This could be the result of chosen inclusion criteria in the various studies. The biggest discrepancy between studies is in the inclusion of cases with chronic villitis. Three different approaches were observed: placentas with co-occurring villitis were excluded [3,7,9,16,29], only placentas with focal villitis were included [2] or placentas with CIUE and villitis were studied [6,7]. Limited evidence is available to exclude cases with villitis. Therefore, cases with CIUE and co-occurring villitis should not be excluded. Presence of fibrin, trophoblastic necrosis, and/or atherosis should also not be required for a diagnosis of CIUE, nor should it rule out the presence of CIUE. Nevertheless, co-occurring histopathological findings in CIUE could provide important insight into the pathophysiology of CIUE and further studies should comprehensively describe the co-occurring histopathological lesions in cases with CIUE.

4.3.3. Excluding infectious causes

Cases with clinical or histopathological signs of infection should be excluded (Criterion IV). In the event of an unfavorable pregnancy outcome (e.g., miscarriage, restricted fetal growth, preterm birth, or stillbirth), most women are screened for the presence of a TORCH infection (toxoplasmosis, treponema pallidum, rubella, cytomegalovirus, herpes virus, and other infections, including varicella, parvovirus B19, HIV, and enteroviruses) [41]. TORCH infections are a major contributor to prenatal, perinatal, and postnatal morbidity and mortality, and should therefore be excluded in the case of CIUE [41]. Furthermore, one should discriminate between a polymorphic infiltrate and a monomorphic infiltrate; a polymorphic infiltrate containing neutrophils and leukocytes is indicative for acute inflammation. Cases with a predominant polymorphic infiltrate should be excluded. A pathologists' finding of evidence of infection is usually scarce; therefore, infectious causes should preferably be excluded based on clinical findings.

4.3.4. Maternal characteristics and obstetric features

In this review, we found that CIUE is reported in mothers of various ages and with a variety of obstetrical histories. Thus, neither the maternal characteristics nor the medical history should necessarily serve as either an inclusion or exclusion criterion. A prospective study should be conducted in order to demonstrate a clear association between the intervillous infiltrate and pregnancy outcome before an adverse pregnancy outcome can be used as an inclusion criterion. Since, associations found between intervillous infiltrates and pregnancy outcome might have been caused by selection bias. Associations between increased levels of maternal serum alkaline phosphatase and CIUE might provide an interesting new diagnostic approach, which should be investigated further [31,42,43].

4.3.5. Future validation

Although consensus does not yet exist regarding these diagnostic criteria, our results set the stage for establishing standardized criteria for diagnosing CIUE. The next step towards understanding the etiology of CIUE is to determine the precise criteria by performing a Delphi study [44]. Thereafter, these criteria should be validated in several patient populations; in a first step towards validation, the pathologists who contributed to the Amsterdam Placental Workshop Group Consensus Statement [40] could assess our proposed diagnostic criteria and examine the cases included in this review. Future studies regarding CIUE should attempt to determine the full spectrum of the syndrome.

5. Conclusions

Here, we propose a set of standardized diagnostic criteria for CIUE, a serious pregnancy complication frequently associated with miscarriage, impaired fetal growth, preterm birth, and a live birth rate of only 54.9%. The relatively high rate of recurrence (25.1%) in subsequent pregnancies and the accompanying pregnancy complications underscore the high clinical relevance of CIUE and the need for further in-depth research.

Financial support

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

Declaration of interest

Conflicts of interest

None.

Acknowledgments

Not applicable.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.placenta.2017.11.012.

References

[1] C. Labarrere, E. Mullen, Fibrinoid and trophoblastic necrosis with massive chronic intervillositis: an extreme variant of villitis of unknown etiology, Am. J. Reprod. Immunol. Microbiol. 15 (3) (1987) 85–91.
[2] O. Parant, J. Capdet, S. Kessler, J. Aziza, A. Berrebi, Chronic intervillositis of unknown etiology (CIUE): relation between placental lesions and perinatal outcome, Eur. J. Obstet., Gynecol. Reprod. Biol. 143 (1) (2009) 9–13.
[3] T.K. Boyd, R.W. Redline, Chronic histiocytic intervillositis: a placental lesion associated with recurrent reproductive loss, Hum. Pathol. 31 (11) (2000) 1389–1396.
[4] B.J. Doss, M.F. Greene, J. Hill, L.J. Heffner, F.R. Bieber, D.R. Genest, Massive chronic intervillositis associated with recurrent abortions, Hum. Pathol. 26 (11) (1995) 1245–1251.
[5] E. Contro, R. deSouza, A. Bhide, Chronic intervillositis of the placenta: a systematic review, Placenta 31 (12) (2010) 1106–1110.
[6] C. Nowak, M. Joubert, F. Jossic, A. Masseau, M. Hamidou, H.J. Philippe, C. Le Vaillant, Perinatal prognosis of pregnancies complicated by placental chronic villitis or intervillositis of unknown etiology and combined lesions: about a series of 178 cases, Placenta 44 (2016) 104–108.
[7] R.W. Bendon, S. Coventry, M. Thompson, E. Rudzinski, E.M. Williams, A.P. Oron, The significance of C4d immunostaining in placental chronic intervillositis, Pediatr. Dev. Pathol. 18 (5) (2015) 362–368.
[8] C.A. Labarrere, E. Bammerlin, J.W. Hardin, H.L. Dicarlo, Intercellular adhesion molecule-1 expression in massive chronic intervillositis: implications for the invasion of maternal cells into fetal tissues, Placenta 35 (5) (2014) 311–317.
[9] C. Capuani, F. Meggetto, I. Duga, M. Danjoux, M. March, O. Parant, P. Brousset, J. Aziza, Specific infiltration pattern of FOXP3+ regulatory T cells in chronic histiocytic intervillositis of unknown etiology, Placenta 34 (2) (2013) 149–154.
[10] A.D. Reus, N.M. van Besouw, N.M. Molenaar, E.A. Steegers, W. Visser, R.P. de Kuiper, R.R. de Krijger, D.L. Roelen, N. Exalto, An immunological basis for chronic histiocytic intervillositis in recurrent fetal loss, Am. J. Reprod. Immunol. (New York, N.Y. 1989) 70 (3) (2013) 230–237.
[11] A. Tchakarov, A. Coffey, N. Tatevian, Neonatal alloimmune thrombocytopenia associated with massive chronic intervillositis: a case report and review of the literature, Pediatr. Dev. Pathol. 16 (1) (2013) 32–34.
[12] E. Dubruc, F. Lebreton, C. Giannoli, M. Rabilloud, C. Huissoud, M. Devouassoux-Shisheboran, F. Allias, Placental histological lesions in fetal and neonatal alloimmune thrombocytopenia: a retrospective cohort study of 21 cases, Placenta 48 (2016) 104–109.
[13] H. Feist, T. Blocker, K. Hussein, Massive perivillous fibrin deposition, chronic histiocytic intervillositis and villitis of unknown etiology: lesions of the placenta at the fetomaternal interface with risk of recurrence, Der Pathol. 36 (4) (2015) 355–361.
[14] J. Ordi, M.R. Ismail, P.J. Ventura, E. Kahigwa, R. Hirt, A. Cardesa, P.L. Alonso, C. Menendez, Massive chronic intervillositis of the placenta associated with malaria infection, Am. J. Surg. Pathol. 22 (8) (1998) 1006–1011.
[15] M. Taweevisit, K. Sukpan, S. Siriaunkgul, P.S. Thorner, Chronic histiocytic intervillositis with cytomegalovirus placentitis in a case of hydrops fetalis, Fetal Pediatr. Pathol. 31 (6) (2012) 394–400.
[16] S.M. Jacques, F. Qureshi, Chronic intervillositis of the placenta, Arch. Pathol. Lab. Med. 117 (10) (1993) 1032–1035.
[17] C. Rota, D. Carles, V. Schaeffer, F. Guyon, R. Saura, J. Horovitz, Perinatal prognosis of pregnancies complicated by placental chronic intervillitis, J. Gynecol. Obstet. Biol. Reprod. Paris. 35 (7) (2006) 711–719.
[18] A. Mekinian, N. Costedoat-Chalumeau, A. Masseau, A. Botta, A. Chudzinski, A. Theulin, V. Emmanuelli, E. Hachulla, C.S. De, A. Revaux, P. Nicaise, F. Cornelis, D. Subtil, F. Montestruc, M. Bucourt, S. Chollet-Martin, L. Carbillon, O. Fain, Chronic histiocytic intervillositis: outcome, associated diseases and treatment in a multicenter prospective study, Autoimmunity 48 (1) (2015) 40–45.
[19] L. Vardi, H. Paterson, N.A. Hung, Successful pregnancy following treatment of recurrent chronic histiocytic intervillositis, BMJ Case Rep. 2017 (2017).
[20] J.S. Lawson, P. Mayberry, How can infant and perinatal mortality rates be compared internationally? World health forum 15 (1) (1994), 85-7; discussion 87–88.
[21] F.C. Battaglia, L.O. Lubchenco, A practical classification of newborn infants by weight and gestational age, J. Pediatr. 71 (2) (1967) 159–163.
[22] G.R. Alexander, M.D. Kogan, J.H. Himes, 1994-1996 U.S. singleton birth weight percentiles for gestational age by race, Hispanic origin, and gender, Matern. Child health J. 3 (4) (1999) 225–231.
[23] N. Suzumori, M. Sugiura-Ogasawara, Genetic factors as a cause of miscarriage, Curr. Med. Chem. 17 (29) (2010) 3431–3437.
[24] R.W. Redline, M. Zaragoza, T. Hassold, Prevalence of developmental and inflammatory lesions in nonmolar first-trimester spontaneous abortions, Hum. Pathol. 30 (1) (1999) 93–100.
[25] L. Bricker, R.G. Farquharson, Types of pregnancy loss in recurrent miscarriage: implications for research and clinical practice, Hum. Reprod. Oxf. Engl. 17 (5) (2002) 1345–1350.
[26] N.S. Macklon, J.P. Geraedts, B.C. Fauser, Conception to ongoing pregnancy: the 'black box' of early pregnancy loss, Hum. Reprod. update 8 (4) (2002) 333–343.
[27] K.S. Joseph, B. Kinniburgh, J.A. Hutcheon, A. Mehrabadi, L. Dahlgren, M. Basso, C. Davies, L. Lee, Rationalizing definitions and procedures for optimizing clinical care and public health in fetal death and stillbirth, Obstet. Gynecol. 125 (4) (2015) 784–788.
[28] K. Hussein, A. Stucki-Koch, H. Kreipe, H. Feist, Expression of toll-like receptors in chronic histiocytic intervillositis of the placenta, Fetal Pediatr. Pathol. (2015) 1–6.
[29] J. Traeder, D. Jonigk, H. Feist, V. Brocker, F. Langer, H. Kreipe, K. Hussein, Pathological characteristics of a series of rare chronic histiocytic intervillositis of the placenta, Placenta 31 (12) (2010) 1116–1119.
[30] L. Freitag, K.C. von, H. Kreipe, K. Hussein, Expression analysis of leukocytes attracting cytokines in chronic histiocytic intervillositis of the placenta, Int. J. Clin. Exp. Pathol. 6 (6) (2013) 1103–1111.
[31] V. Marchaudon, L. Devisme, S. Petit, H. Ansart-Franquet, P. Vaast, D. Subtil, Chronic histiocytic intervillositis of unknown etiology: clinical features in a consecutive series of 69 cases, Placenta 32 (2) (2011) 140–145.
[32] D.S. Heller, CD68 immunostaining in the evaluation of chronic histiocytic intervillositis, Arch. Pathol. Lab. Med. 136 (6) (2012) 657–659.
[33] C.A. Labarrere, J.W. Hardin, D.M. Haas, G.S. Kassab, Chronic villitis of unknown etiology and massive chronic intervillositis have similar immune cell composition, Placenta 36 (6) (2015) 681–686.
[34] A. Revaux, A. Mekinian, P. Nicaise, M. Bucourt, F. Cornelis, E. Lachassinne, S. Chollet-Martin, O. Fain, L. Carbillon, Antiphospholipid syndrome and other autoimmune diseases associated with chronic intervillositis, Arch. Gynecol. Obstet. 291 (6) (2015) 1229–1236.
[35] S. Sabra, C.R. Zurriaga, A. Saborit, M.D. G+¦-mez Roig, A series of rare chronic histiocytic intervillositis cases and its association with fetal growth restriction, Gynecol. Obstet. Res. Open J. 3 (2) (2016) 26–31.
[36] A. Rammes, J. Roth, M. Goebeler, M. Klempt, M. Hartmann, C. Sorg, Myeloid-related protein (MRP) 8 and MRP14, calcium-binding proteins of the S100 family, are secreted by activated monocytes via a novel, tubulin-dependent pathway, J. Biol. Chem. 272 (14) (1997) 9496–9502.
[37] M. Goebeler, J. Roth, S. Teigelkamp, C. Sorg, The monoclonal antibody MAC387 detects an epitope on the calcium-binding protein MRP14, J. Leukoc. Biol. 55 (2) (1994) 259–261.
[38] M.S. Kramer, M.F. Chen, I. Roy, C. Dassa, J. Lamoureux, S.R. Kahn, H. McNamara, R.W. Platt, Intra- and interobserver agreement and statistical clustering of placental histopathologic features relevant to preterm birth, Am. J. Obstet. Gynecol. 195 (6) (2006) 1674–1679.
[39] E.A. Steegers, P. von Dadelszen, J.J. Duvekot, R. Pijnenborg, Pre-eclampsia, Lancet (London, Engl. 376 (9741) (2010) 631–644.
[40] T.Y. Khong, E.E. Mooney, I. Ariel, N.C. Balmus, T.K. Boyd, M.A. Brundler, H. Derricott, M.J. Evans, O.M. Faye-Petersen, J.E. Gillan, A.E. Heazell, D.S. Heller, S.M. Jacques, S. Keating, P. Kelehan, A. Maes, E.M. McKay, T.K. Morgan, P.G. Nikkels, W.T. Parks, R.W. Redline, I. Scheimberg, M.H. Schoots, N.J. Sebire, A. Timmer, G. Turowski, J.P. van der Voorn, I. van Lijnschoten, S.J. Gordijn, Sampling and definitions of placental lesions: Amsterdam placental Workshop group consensus statement, Arch. Pathol. Lab. Med. 140 (7) (2016) 698–713.
[41] N. Neu, J. Duchon, P. Zachariah, TORCH infections, Clin. Perinatol. 42 (1) (2015) 77–103 viii.
[42] I. Das, S. Thamban, N. Agarwal, Chronic histiocytic intervillositis-a rare placental inflammatory disease associated with poor obstetric outcome and elevated maternal serum alkaline phosphatase: A case report, BJOG: An International Journal of Obstetrics and Gynaecology Conference: RCOG World Congress 2013 Liverpool United Kingdom. Conference Start: 20130624 Conference End: 20130626. Conference Publication: (var.pagings) (2013) 155.
[43] J.E. Dahlstrom, C.J. Nolan, R. McCormack, A. Gordan, Pediatric and Perinatal Pathology: SY21–1 CHRONIC INTERVILLOSITIS: VALUE of ALKP MONITORING. [Miscellaneous], Pathology 46 Abstracts, 2014. XXXth-S33.
[44] I.R. Diamond, R.C. Grant, B.M. Feldman, P.B. Pencharz, S.C. Ling, A.M. Moore, P.W. Wales, Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies, J. Clin. Epidemiol. 67 (4) (2014) 401–409.