



Towards standardized criteria for diagnosing chronic intervillitis 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

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ABSTRACT

Chronic intervillitis 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.

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ABBREVIATIONS: CIUE, chronic intervillitis 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).

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1. Introduction

Chronic intervillitis of unknown etiology (CIUE) is a poorly understood, relatively rare condition first described in 1987 by Labarrere and Mullen as massive chronic intervillitis. They defined massive chronic intervillitis 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 intervillitis 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 intervillitis by Labarrere and Mullen, a variety of terms have been used to describe this condition, including “*chronic intervillitis of unknown etiology*”, “*chronic intervillitis*”, “*chronic histiocytic intervillitis of unknown etiology*”, “*chronic histiocytic intervillitis*”, “*massive histiocytic chronic intervillitis*”, “*massive perivillous histiocytosis*”, “*intervillitis*”, and “*massive chronic intervillitis*” [8]. It is important to distinguish between chronic intervillitis referring to a histologic placenta lesion irrespective of the cause, and the specific condition we define. The term “chronic intervillitis 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 intervillitis 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 intervillitis 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

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