

1. Abstract

Background: Chronic Histiocytic Intervillositis (CHI) is a rare inflammatory lesion in the placenta strongly associated with foetal growth restriction and pregnancy loss. It's diagnosable after birth by placental histological analysis and its high recurrence rate has major clinical significance.

Methods: A literature review was performed of Pubmed, Medline and Web of Science databases to assess how patients with CHI pregnancies are detected, monitored and treated.

Results: Raised alkaline phosphatase (ALP) was reported as in association with CHI in 5 papers, however being elevated in only 30-61% of cases gives it a low specificity. Aspirin (ASA), prednisolone and hydroxychloroquine are the medications most frequently linked to positive outcomes but efficacy is unproven. Regular ultrasound monitoring of subsequent CHI pregnancies is recommended in clinical management but rarely documented in research studies.

Conclusions: Longitudinal studies of serum proteins and imaging parameters would aid our understanding of the natural history of CHI, and may identify prognostic biomarkers. Randomised controlled trials for drug pharmacological treatments are needed.

2. Introduction

Definition

CHI describes a pattern of mainly histiocytes (white blood cells) and fibrin deposits in the intervillous space of the placenta that was first identified by Labarrere in 1987(1). Standardised diagnostic criterion has been proposed by Bos et al., 2018(11).

Chronic Intervillositis (CI)

Chronic Histiocytic Intervillositis ("**CHI**")
"**CIUE**" or "**MCI**"
Maternal Histiocytes

Chronic Villitis (CV)

Chronic Villitis of Unknown Etiology (**CVUE**)
Fetal Lymphocytes

Figure 1. CI and CV are separate pathologies. CIUE: Chronic Intervillositis of Unknown Etiology. MCI: Massive Chronic Intervillositis

Epidemiology

An immunological origin has been theorised for CHI(1)(5)(6) and the suggested association with maternal alloimmunization against human platelet antigen(HPA)(8)(9) has received some supportive investigations (2)(7). Prevalence is reported at 1/3666 births(10), 1/1000 miscarriages and 1/1667 stillbirths(6). Recurrence rate reports range from 18–67%(6)(14) in retrospective studies, 80% in 2010 systematic review (15), and almost 30% in the only prospective study(16).

Effect on Obstetric Outcomes

The adverse outcomes reportedly linked to CHI include maternal hypertension(3), HELLP Syndrome(17), foetal growth restriction (FGR), miscarriage, stillbirth, termination of pregnancy and neonatal death (4)(10)(12)(13)(14)(18)(19). Preterm delivery reported in association with CHI has its own complications and is often indicated due to severe FGR (5)(6)(14)(16)(20).

3. Method

Research Strategy

OVID Medline, PubMed and Web of Science databases that reported on "Intervillositis".

Included studies were assessed for three key areas:

- Biochemical markers:** ALP, Pregnancy Associated Plasma Protein-A (PAPP-A), maternal serum alpha-fetal protein
- Imaging techniques:** Doppler Ultrasound (US), Magnetic Resonance Imaging (MRI)
- Pharmacological Treatments:** ASA, Low Molecular Weight Heparin (LMWH), immunomodulators.

Criteria

Inclusion	Exclusion
Published 2000-2021	Published before 2000
Publications written in English	Non-English Publication
Massive Chronic Intervillositis	Villitis of Unknown Etiology (VUE)
Chronic histiocytic Intervillositis Chronic Intervillositis of Unknown Etiology (CIUE)	Associated with Infection CiuE Protein

4. Results

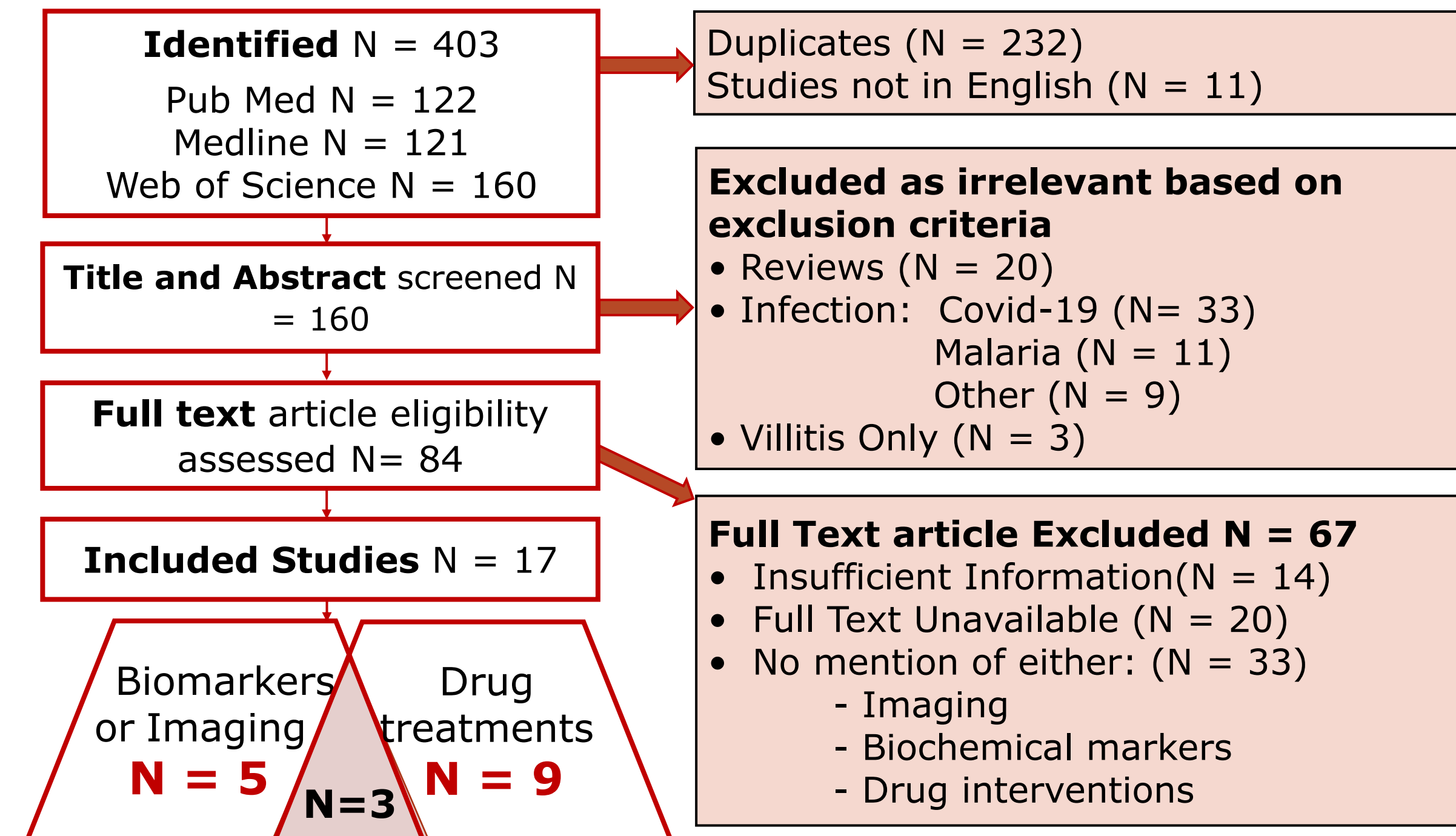


Figure 2. Flow diagram for Study Selection

Biomarkers and Imaging

From the 84 papers fully assessed, ALP was measured in 6 papers and 5 of these found it to be elevated in 30-61% of CHI cases (12)(13)(14)(16)(21). Koby(22), Sauvestre(21), and Homatter(12) also analysed PAPP-1, beta-hCG, AFP, inhibin-A, and ME3.

There was a substantial lack of detail on the recommended imaging techniques(26) with US referenced in 5/84 papers.

Pharmacological Therapies

The main treatments identified in this review were anticoagulants (LMWH), anti-platelets (Aspirin), and immunomodulators (Prednisolone and Hydroxychloroquine) however the impact of these on the rate of adverse pregnancy outcome lacks evidence.

Contrary to small case reports presenting treatment success(20), a correlation between treated CHI cases and worse obstetric outcomes was concluded by systematic review(15). None of the analyses performed in Homatter's(12) case-control study or Mattuizzi's (19) case series indicate a benefit from aspirin, LMWH, corticosteroids or intravenous immunoglobulins (IVI) and azathioprine.

5. Discussion

Monitoring and Treating CHI

ALP can be elevated in uncomplicated pregnancies and normal reference ranges for each trimester have been determined (25). Marchaudon 2011(14) attributed increased ALP to histocytes in the intervillous space producing syncytio-trophoblastic lesions before fibrin deposits cover them. The diagnosis of FGR according to Delphi procedure includes doppler US end diastolic flow in the umbilical and/or uterine artery(23), yet of the 84 papers assessed for imaging techniques, only 5 specify the findings of doppler US. Ozawa et al. 2017(24) was the only paper to describe MRI findings in a case report on a single patient with 3 experiences of CHI. The progressive impairment of maternofetal exchanges(14) due to fibrin deposition following histiocytic lesion development in CHI affect the diffusivity and oxygenation of the placenta which could be measured by MRI as described by Aughwane et al 2019(27).

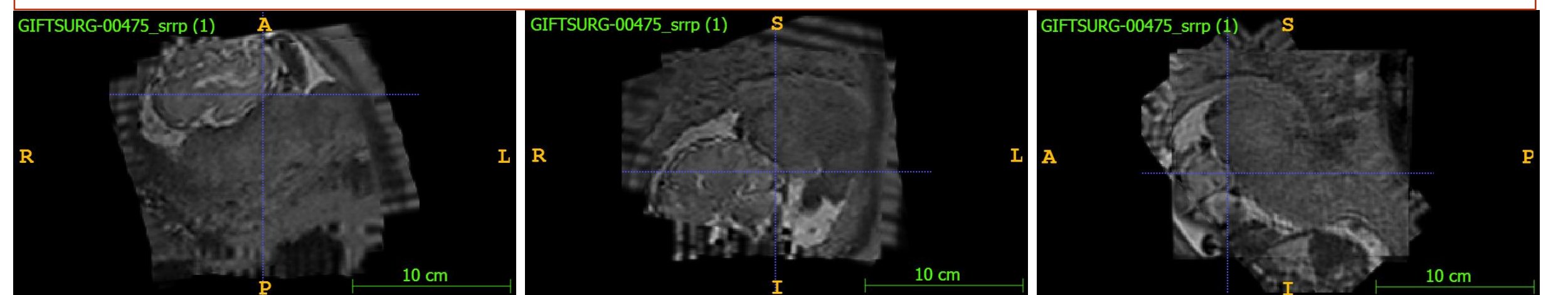


Figure 3: MRI of the placenta in a case of CHI provided by Dr. Andrew Melbourne, KCL, shown using the ITK-SNAP software(28)

6. Conclusions

Studies of CHI are limited by small samples sizes due to the rarity of the disease. There are currently no reliable diagnostic or prognostic markers. More data from multicentre epidemiological studies could aid the search for biomarkers and maternal prognostic factors. Prospective longitudinal studies of serum proteins and ultrasound and MRI would improve our knowledge of the natural history of CHI, and may identify useful prognostic biomarkers. Ideally larger prospective Randomised Control Trials on treatments are needed to prove the association between specific drugs and positive obstetric outcomes.

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