Haemophagocytic lymphohistiocytosis in pregnancy and the postpartum period: A retrospective case series analysis

[version 1; peer review: 2 approved]

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Abstract

Introduction: Haemophagocytic lymphohistiocytosis (HLH) is an extremely rare condition characterised by excessive immune activation leading to haemophagocytic activity and has seldom been reported in pregnancy. HLH manifests as relapsing fevers with features of multi-organ failure and has a high mortality.

Methods: A retrospective case series analysis using national data from MBRRACE-UK maternal death reports (n=5) and case notes from patients diagnosed with HLH during pregnancy at New Cross Hospital, Wolverhampton (n=2) between 2012 and 2021.

Results: A total of seven cases were included. Cases uniformly presented with fever and experienced prodromal illnesses consisting of lymphadenopathy, fevers, and malaise. Gestation at presentation ranged from 9/40 to 11 months postpartum. All patients had multiple cytopenias. Other common features included elevated liver enzymes (n=5), hyperferritinaemia (n=5), splenomegaly (n=4), hypofibrinogenemia (n=4) and elevated soluble interleukin-2 receptor α (CD25) levels (n=3). Underlying causes were identified in four cases. Median time from presentation to diagnosis was 35 days. Bone marrow biopsy was diagnostic in a majority of cases. Corticosteroids and ciclosporin were the most frequently used treatments. In some cases early delivery by caesarean section or termination of pregnancy was necessary to permit maternal treatment. Progression to multi-organ failure resulting in maternal death occurred in five cases: two cases survived. Pregnancy outcomes were: livebirth at term (n=2), preterm livebirth (n=3), termination of pregnancy (n=1), and miscarriage (n=1). Of the surviving infants, one had bone marrow suppression with anaemia at birth and sensorineural deafness.

Conclusions: Due to the rarity of the condition, diagnosis is often delayed. In view of the high mortality, clinicians should consider HLH early when reviewing pregnant patients with unexplained pyrexia and
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multi-organ dysfunction. Early involvement of haematology should be sought, as prompt diagnosis is crucial for meaningful attempts at curative therapy. Important treatment considerations include fetal viability, maternal condition and treatment toxicity.

Keywords
Case series, haemophagocytic lymphohistiocytosis, pregnancy, fever of unknown origin
Plain English summary

Haemophagocytic lymphohistiocytosis (HLH) is an extremely rare and life threatening condition. It is a disorder where the body reacts to any stimulus which produces an excessive immune response causing severe inflammation and damage to multiple major organs. If not diagnosed and treated on time, it can lead to major organ failure and even death.

HLH affecting pregnant women can be life threatening affecting both mother and the baby. Early diagnosis and treatment by specialist teams of doctors can help in improving the outcomes. Our case series aims to bring awareness about this serious disorder, so that it can be identified early and treated accordingly.

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is characterised by the coexistence of immune dysregulation and unchecked inflammation, leading to haemophagocytic activity. It has seldom been reported in pregnancy. Clinically HLH manifests as relapsing fevers with features of multi-organ failure. The mortality rate from HLH is estimated at 50% even with optimal treatment. Therefore, prompt investigation and diagnosis are essential for meaningful attempts at curative therapy.

Case presentation

This retrospective case series analysis uses all national maternal death reports reported to MBRRACE-UK attributed to HLH between 2012 and 2021, and case notes from two patients diagnosed with HLH during pregnancy. The objective is to describe the presentation, diagnosis, management, and maternal and fetal outcomes of these cases.

Demographics

A total of seven cases were included, of which five were maternal deaths and two survivors. Median maternal age at presentation was 30 years and ranged from mid-20’s to mid-30’s. Initial presentation occurred during pregnancy in six cases. The remaining case presented during the postnatal period. Of the cases that presented during pregnancy, three were primigravidae. The obstetric histories of the remaining cases were unremarkable, apart from one woman who had fetal growth restriction in a previous pregnancy. The majority of women were previously fit and well with no significant medical history, although one had a history of inflammatory arthritis.

Presentation

The women uniformly presented with pyrexia and experienced prodromal illnesses of varying durations (range: three days – nine weeks) consisting of lymphadenopathy, fevers and malaise. The timing of presentation ranged from nine weeks gestation to 11 months postpartum. One patient received a preliminary diagnosis of Kikuchi lymphadenitis after experiencing a prolonged prodrome of cervical lymphadenopathy, fevers and weight loss. Other symptoms manifesting at the time of presentation included pruritis [n=4], skin rash [n=3], shortness of breath [n=3] and arthropathy [n=2].

Investigations

Diagnosis

All women had multiple cytopaenias and fulfilled the HLH-2004 diagnostic criteria for HLH. In order to be recognised as HLH, patients must fulfil five of the eight diagnostic criteria. These are listed in Table 1 along with the number of women who fulfilled each criterion.

Common features included elevated liver enzymes [n=5], hyperferritinaemia [n=5], splenomegaly [n=4], hypofibrinogenemia [n=4] and elevated soluble interleukin-2 receptor α (CD25) levels [n=3]. It should be noted, however, that soluble CD25 levels were not measured in three women, and ferritin was not measured in one woman. Peripheral blood cytopaenias were often severe with completely obliterated white cell counts leading to recurrent infections that necessitated significant blood product support with packed red cells and platelet infusions.

All cases were extensively investigated before a definitive diagnosis was reached. Patients had repeated samples of blood, urine and sputum sent for culture, in addition to plain film imaging of the chest to identify a source of infection. Women also underwent ultrasound imaging to investigate the cause of lymphadenopathy and organomegaly. In addition, CT and MRI imaging was used to rule out malignancy.

Underlying causes were identified in five cases, infection [n=3], rheumatological disease [n=2] and sickle cell crisis [n=1]. Infections included bacterial urosepsis, Epstein Barr viral hepatitis and symptomatic cytomegalovirus reactivation. One woman had a pre-existing diagnosis of inflammatory arthritis, which was believed to trigger HLH, and a further case was diagnosed with it during investigations for the cause of their HLH.

The median time from presentation to diagnosis was 35 days. One case was diagnosed postmortem as the disease rapidly progressed to multi-organ failure before a diagnosis could be made. Excluding that case, all women had a bone marrow aspiration and haemophagocytosis was visible on histological examination. One sample was not diagnostic on first aspiration and was repeated several weeks later. The repeat sample was conclusive. Histological findings generally prompted definitive diagnosis of HLH. Table 2 summarises the cases.

Treatment

After the diagnosis of HLH had been made, corticosteroids and ciclosporin were the most frequently used treatments. Dexamethasone was administered intravenously per the HLH-2004 protocol, with an initial dose of 10 milligram(mg)/metre(m)$^2$ and subsequently tapered. Prior to definitive diagnosis, corticosteroids were administered orally or intravenously and included hydrocortisone, dexamethasone, prednisolone and methylprednisolone. The cytotoxic agent, ciclosporin, was administered orally at a dose of 6 mg/kg daily in two divided doses and titrated to achieve a target serum trough level of 200 microgram/litre(L).
Table 1. Women meeting each of the HLH-2004 diagnostic criteria.

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>Number of women (total = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &gt; 38.5</td>
<td>7</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>4</td>
</tr>
<tr>
<td>Peripheral blood cytopaenias (2/3 of: haemoglobin &lt;90 g/L, platelets &lt;100 x10⁹/L, neutrophils &lt;1 x10⁹/L)</td>
<td>6</td>
</tr>
<tr>
<td>Hypertriglyceridaemia (&gt;3 mmol/L) and/or hypofibrinogenemia (&lt;1.5 g/L)</td>
<td>4</td>
</tr>
<tr>
<td>Haemophagocytosis seen on biopsy of bone marrow/spleen/lymph nodes</td>
<td>7</td>
</tr>
<tr>
<td>Low or absent natural killer (NK) cell activity</td>
<td>1</td>
</tr>
<tr>
<td>Ferritin &gt;500 ng/ml</td>
<td>5</td>
</tr>
<tr>
<td>Soluble interleukin-2 receptor α (CD25) &gt;2400 U/ml</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2. Tabulated timeline and overview of the HLH cases.

<table>
<thead>
<tr>
<th>Case ID</th>
<th>Onset of symptoms</th>
<th>Time to diagnosis</th>
<th>Therapies</th>
<th>Maternal outcome</th>
<th>Fetal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Presented first trimester with a 24-hour history of itching, ecchymoses and abdominal pain</td>
<td>35 days</td>
<td>Anti-infective drugs, Steroids, Cyclosporin, IVIG*, Rituximab, Etoposide</td>
<td>Died – 2 months after presentation</td>
<td>Pregnancy ended at 21 weeks</td>
</tr>
<tr>
<td>2</td>
<td>First trimester presented with neck swelling, night sweats, fevers, and weight loss</td>
<td>107 days</td>
<td>Anti-infective drugs, Steroids, Cyclosporin, IVIG*, Etoposide</td>
<td>Died – 8 months after presentation</td>
<td>Live baby born at 24 weeks gestation. The baby survived.</td>
</tr>
<tr>
<td>3</td>
<td>Presented in the second trimester with a history of dyspnoea, cough and fatigue and anaemia</td>
<td>16 days</td>
<td>Anti-infective drugs, Steroids, Cyclosporin, Methotrexate, IVIG* Etoposide</td>
<td>Died – 2 months after presentation</td>
<td>Second trimester miscarriage.</td>
</tr>
<tr>
<td>4</td>
<td>Presented 11 months postpartum with right sided neck swelling. Two weeks later developed sweats, peri-auricular and joint swelling</td>
<td>Diagnosed post-mortem</td>
<td>Anti-infective drugs, Steroids</td>
<td>Died – 17 days after presentation</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>Presented in the second trimester with high grade fever, pain in upper abdomen and feeling unwell. Low platelets and deranged liver function tests</td>
<td>15 days</td>
<td>Antibiotics, Antifungals, Steroids, Anakinra</td>
<td>Alive and well</td>
<td>Live baby born by emergency caesarean section at 31+5 gestation.</td>
</tr>
<tr>
<td>6</td>
<td>Presented in the second trimester with fever, a urinary tract infection and arthropathy. Raised CD25 count, a very high Ferritin level and low platelets</td>
<td>20 days</td>
<td>Antibiotics, Steroids</td>
<td>Alive, developed Still’s disease</td>
<td>Live baby born vaginally at 37 weeks gestation.</td>
</tr>
<tr>
<td>7</td>
<td>Presented in the third trimester with acute sickle cell crisis, fever, and bony pains.</td>
<td>22 days</td>
<td>Blood transfusion, Antibiotics</td>
<td>Died – 25 days after presentation</td>
<td>Spontaneous preterm birth.</td>
</tr>
</tbody>
</table>

*IVIG intravenous immunoglobulin
Women also received intravenous (IV) antibiotics, antivirals and antifungals, either in response to proven or clinically suspected infection, or as prophylaxis due to immunocompromise. Antibiotic medications included: co-amoxiclav, teicoplanin, gentamicin, meropenam, piperacillin/tazobactam, metronidazole, vancomycin and amikacin. Prophylactic co-trimazole cover against *Pneumocystis jiroveci* was prescribed for two women. Antivirals included: aciclovir, tenofovir disoproxil, ganciclovir and lamivudine. Antifungals utilised were fluconozole and caspofungin. Choice and dose of antimicrobials varied according to clinical judgement and local policy. Good response to treatment of underlying infection was achieved in one case.

IV immunoglobulins were prescribed for three women (0.5 milligrams/kilogram IV once every 4 weeks), and one woman was treated with Anakinra (100 milligrams daily by subcutaneous injection). Due to the severity of the maternal condition and failed attempts at other therapies, early delivery by caesarean section was undertaken in two women (between 24–32 weeks of gestation) and termination of pregnancy in one case. Delivery or termination permitted aggressive maternal treatment with agents that are considered unsafe during pregnancy including etoposide and other cytotoxic agents. Etoposide was administered IV at a dose of 150mg/m². Allogenic haemopoietic stem cell transplantation was undertaken in one case post-delivery.

**Outcome and follow up**

Admission to level three critical care units was necessary for six women, with the duration of stay ranging from 1 day to 231 days. These women required multi-organ support including invasive ventilation, haemofiltration and inotropic medications. Sadly, five women progressed to multi-organ failure resulting in maternal death; two women survived. The recorded causes of death were multi-organ failure [n=2], acute respiratory distress syndrome (ARDS) [n=1] and sepsis [n=1]; all of which were associated with concomitant HLH.

There were two livebirths at term, two preterm livebirths, one woman had a termination of pregnancy and one a spontaneous miscarriage. One surviving infant, whose mother had received Anakinra, an interleukin inhibitor, during pregnancy, had bone marrow suppression with anaemia at birth and was later diagnosed with sensorineural deafness. Given the timing of the development of the fetal anaemia, it is possible that the bone marrow suppression may have been a result of the Anakinra, although it is impossible to rule out other causes, such as HLH itself, given the lack of published data in pregnancy.

**Discussion**

HLH is an immune disorder which results in an ‘inflammatory storm’. Known triggers include infection, malignancy, rheumatological and autoimmune conditions. It can also occur spontaneously and it has been suggested that it can be precipitated by pregnancy itself. The women in this series uniformly presented with pyrexia after a prodromal phase of variable duration. All fulfilled the diagnostic criteria for HLH and six of the women were admitted to level 3 critical care with multi-organ failure. Successful treatment is reliant upon early diagnosis and suppression of the excessive inflammatory reaction.

Due to the rarity of the condition, particularly during pregnancy, diagnosis is often delayed⁶. With diagnostic delays meaning the disease may be in advanced stages at diagnosis. In addition to the need to consider the impact of treatment on the fetus, there can be other dilemmas in the management of these cases leading to prolonged delays in initiating effective treatment⁷. Early multi-disciplinary team (MDT) involvement can facilitate prompt formulation of appropriate management plans. Additionally, in view of the high mortality, clinicians should consider HLH early when reviewing pregnant patients with unexplained pyrexia and multi-organ dysfunction, with a low threshold for additional investigations.

Reaching a correct diagnosis is an obstetric challenge. The blood results of HLH are nonspecific⁸. Hyperferritinaemia with a ferritin above 500ng/ml in adults is a non-specific diagnostic feature, which can be found in many disease conditions, but a ferritin level >10,000ng/L is significantly higher than would be expected in inflammatory syndromes or sepsis⁹. Pronounced hyperferritinaemia in the setting of systemic signs and symptoms along with a negative infectious and rheumatological workup should raise suspicion of HLH⁷. Where clinical suspicion is high, treatment should be commenced, as delaying treatment while awaiting results of investigations to confirm the diagnosis may be detrimental⁹.

The women presented in this paper were extensively investigated due to diagnostic uncertainty, and in the majority of instances it was bone marrow biopsy which confirmed the diagnosis of HLH. Histological examination of lymphoid tissue, such as bone marrow, lymph nodes, liver, or spleen, may show haemophagocytosis, which describes the engulfment of hematopoietic cells by activated macrophages acting outside of usual immune system regulations¹⁰. However, despite the fact that haemophagocytosis is prominently featured in the name of this disease, early on in the natural history of the disease, biopsies may be normal or demonstrate nonspecific findings such as increased or decreased unilineage or multilineage hematopoiesis; haemophagocytosis may not be present until later in the disease process. As in one of our reported cases, repeated bone marrow biopsies may be necessary to demonstrate the characteristic findings and repeated samples should be considered where clinical suspicion is high, yet the diagnosis remains uncertain. Early involvement of haematology expertise should be sought, as prompt diagnosis is crucial for meaningful attempts at curative therapy. These data do not allow any inferences to be made about why some women died when others survived. However, from the general literature, an early diagnosis followed by prompt treatment is of benefit to patients.

Other investigations more specific to HLH are detectable earlier in the disease process. Mayama et al. suggest that measuring
soluble CD25 levels is the most specific diagnostic criteria for HLH, due to the direct correlation with increased T-cell and natural killer (NK) cell activity. Soluble CD25 levels were not measured in three of the cases presented in this paper, and we suggest that this investigation should be considered in any case where HLH is suspected.

Adult-onset Still’s disease (AOSD) is an autoimmune condition that can predispose patients to developing HLH. Therefore, the opinion of an expert rheumatologist is valuable when assessing patients suspected of having HLH. In this series of cases, one patient had a diagnosis of AOSD prior to becoming pregnant, and another was diagnosed with AOSD after being treated for HLH. One woman experienced multiple episodes of sepsis following a mid-trimester miscarriage. Despite aggressive treatment with antibiotics and immunosuppressive therapy she died.

A small number of published case reports have highlighted the association between AOSD and HLH in pregnancy. Dunn et al. reported a case of a woman in her early 40’s with history of Still’s disease, who was admitted with high grade fever at 19 weeks’ gestation and subsequently diagnosed with HLH. This patient responded well to steroids and the disease remained in remission for the rest of the pregnancy. Peters et al. reported a case report of new-onset adult-onset Still’s disease in a woman in her mid-20’s at 35 weeks’ gestation, which presented as macrophage-activation syndrome. Her condition improved with immunosuppressive therapy and the fetus was delivered prior to treatment. There are also two cases reported of neonatal HLH associated with maternal AOSD.

Treatment of HLH in pregnancy poses a number of challenges. There are several important considerations including fetal viability, maternal condition, treatment toxicity and identification of any triggers towards which specific treatments can be directed. There is no universally agreed treatment for HLH in pregnancy, controlling and removing the underlying cause is a priority. Infections should be treated initially with broad spectrum antibiotics, narrowing to bacteria specific when sensitivities are available. Similarly, rheumatological and autoimmune conditions and lymphoid malignancies should have disease specific treatment. Supportive treatment with blood products is also often necessary. Treatment options directed at HLH include IV and oral steroids, IV immunoglobulins (IVIG), cytotoxic drugs, Etoposide, Anakinra (a recombinant IL-1 receptor antagonist) and highly active antiretroviral therapy (HAART). HLH has also been treated with bone marrow transplant (BMT).

Although Etoposide is both embryotoxic and teratogenic, in catastrophic cases it has been suggested that the benefit likely outweighs the potential harm to the fetus and should be strongly considered, and favourable outcomes after etoposide treatment during pregnancy have been reported. In the cases presented in this paper, early delivery of viable fetuses to allow maternal treatment with Etoposide was favoured over the risks of treatment during pregnancy.

One case received an allogenic BMT following delivery of her infant, but despite an initial promising response continued to suffer multiple septic episodes, recurrent gastrointestinal bleeds, acute kidney failure and profound electrolyte disturbances. This patient eventually died from ARDS.

There are limited studies showing long term effects of Anakinra on the fetus if used during pregnancy, although there are reports of successful use of Anakinra with favourable fetal and maternal outcomes. Anakinra was used in one of our patients with a favourable maternal response, however the fetus had bone marrow suppression at birth and long term follow up of the baby revealed sensorineural deafness. It is thought this was due to the use of Anakinra, but other causes are possible, including HLH itself.

In summary, it is important to consider HLH as a potential diagnosis when reviewing pregnant patients with unexplained fever and multi-organ dysfunction, to avoid delays in diagnosis and treatment initiation. Early MDT involvement can facilitate prompt diagnosis and identification of underlying causes. Treatment should be directed against the underlying cause where one is identified, and the risks of treatment toxicity need to carefully weighed against the benefits. Early delivery may permit aggressive maternal treatment in catastrophic cases.

Patient perspective
The following quote describes the experience of a woman diagnosed with HLH in pregnancy at the height of the pandemic. It describes the fear and helplessness that she felt at the time.

“It was a very difficult time for me as I was critically ill and all by myself.

Due to the pandemic, no one from my family could visit me and I could not see my husband or children at home. I was scared about my pregnancy when I came to know how critically ill, I was.

I cried thinking about my family and the thought that I might not be able to see them again scared me.

I feared for my baby and this pregnancy.

I was not taken seriously by my GP or A&E doctors when I repeatedly told them how poorly I felt and when I presented to the hospital.

I am extremely thankful to all the doctors, midwives and other staff on maternity who looked after me while I was admitted. I was so relieved and thankful when my baby was born. I totally understand the seriousness of the condition and find myself extremely lucky to have a safe and successful outcome of pregnancy.”
Conclusions
Haemophagocytic lymphohistiocytosis should be considered in the differential diagnosis in any pregnant woman who presents with a relapsing fever and incipient or overt multi-organ failure. Although identification of haemophagocytosis on a bone marrow biopsy is diagnostic, this may only appear later in the course of the disease, therefore repeated biopsy may be necessary. Any underlying causes in secondary HLH must be treated promptly and effectively. Management of women with HLH requires a multi-disciplinary approach, with involvement of obstetrics, rheumatology, haematology and critical care. Long term follow-up is required to ensure the continued health of the mother and to detect any adverse consequences of the disease, or treatment, in the children.

Data availability
All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines
Figshare: CARE checklist for 'Haemophagocytic lymphohistiocytosis in pregnancy and the postpartum period: A retrospective case series analysis' [https://doi.org/10.6084/m9.figshare.2186786v23].

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).
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Shonag Mackenzie
Obstetrics & Gynaecology, Borders General Hospital, Melrose, Scotland, UK

This article describes 7 cases of haemophagocytic lymphohistiocytosis (HLH) in pregnancy in the UK. As a rare life-threatening condition raising awareness of this condition is important.

Areas for discussion or outlined below.

Plain English Summary and Introduction:

- An explanation here that this is secondary HLH or adult HLH would have been useful.

- It would have been more informative if the authors had referenced the paper by Liu et al. Liu C, Gao J, Liu J: Management of hemophagocytic lymphohistiocytosis in pregnancy: Case series study and literature review. J Obstet Gynaecol Res. 2022; 48 (3): 610-620

- A comparison between the management of the women in the UK and those in China and outcomes would have added to knowledge on how to manage this rare condition.

Discussion:

- Improved references and discussion of treatments regarding their effects on the fetus would strengthen the article.

- “The cytotoxic agent, ciclosporin” is this considered cytotoxic?

- Regarding Anakinra.....“the fetus had bone marrow suppression at birth and .....sensorineural deafness. It is thought this was due to the use of Anakinra, but other causes are possible, including HLH itself.”
  - What evidence do the authors have to reach this conclusion?

- This article may have been a useful reference.
I highlight this as a recurring theme in the MBRRACE reports is failure to give adequate treatment to pregnant women due to fear of the effects on the fetus and the mortality for women with this condition is high.

A strength of this paper is including the patient perspective which is powerful.

References

Is the background of the cases' history and progression described in sufficient detail? Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes? Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment? Partly

Is the conclusion balanced and justified on the basis of the findings? Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: The critically ill pregnant patient, maternal mortality and morbidity surveillance

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 03 March 2023
https://doi.org/10.3310/nihopenres.14465.r29045

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Stephen E. Lapinsky
This article describes Haemophagocytic lymphohistiocytosis in pregnancy, using 5 cases from MBRRACE-UK maternal deaths and 2 local cases. That this somewhat enigmatic and poorly understood condition can occur related to pregnancy is an important message for those who care for pregnant persons. The article is clear and well written, and a valuable contribution to the literature. I have only a few questions of clarification.

**Investigations:**
- It is mentioned that "All cases were extensively investigated..." Was there any suggestion identified of limitations to investigation related to the pregnant state (eg. radiological imaging, bone marrow aspirate), which may delay diagnosis?
- You comment on the sensitivity of the finding of haemophagocytosis (and that early testing may be negative) but can you comment on the specificity - is this a diagnostic test for HLH?

**Treatment**
- You state "The cytotoxic agent, ciclosporin,..." - is ciclosporin cytotoxic?
- Can you describe how many patients actually received etoposide?

**Discussion**
- You comment, "There is no universally agreed treatment for HLH in pregnancy", While this is true, I believe it could be expanded that there is no agreed treatment in adults, and much of the diagnostic and treatment literature in HLH is derived from Paediatric studies.

**Is the background of the cases' history and progression described in sufficient detail?**
Yes

**Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?**
Yes

**Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?**
Yes

**Is the conclusion balanced and justified on the basis of the findings?**
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Critical illness during pregnancy

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.