Management of hemophagocytic lymphohistiocytosis in pregnancy

Congcong Liu

Peking Union Medical College Hospital

Jinsong Gao

Peking Union Medical College Hospital

Juntao Liu (✉ liujtpumch@sina.com)

Peking Union Medical College Hospital <https://orcid.org/0000-0002-7021-8211>

Research

Keywords: Hemophagocytic lymphohistiocytosis, Pregnancy, Corticosteroid, Etoposide

Posted Date: January 22nd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-24729/v2>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background: The diagnosis of hemophagocytic lymphohistiocytosis (HLH) in pregnancy is challenging due to its rarity. There is currently no consensus on the treatment of HLH during pregnancy. We aim to analyze and summarize the clinical characteristics of HLH in pregnancy, and to discuss effective diagnostic and treatment options.

Methods: Thirteen patients with HLH during pregnancy who were diagnosed and treated at the Peking Union Medical College Hospital of the Chinese Academy of Medical Sciences from January 2000 to December 2019 were studied retrospectively. We collected data on treatment regimens and on maternal and pregnancy outcomes.

Results: All patients had a singleton pregnancy, with a median age of 28 years (range, 22–33 years) and a median gestational age of 23 weeks (7–36 weeks). There were underlying associated diagnoses in six patients; of the patients, 12 (92.3%, 12/13) were treated with corticosteroids, and a good efficiency was achieved in 5 (41.7%, 5/12) of them. Two patients who were treated with dexamethasone and etoposide after termination of pregnancy achieved CR. Two patients attained remission after termination of pregnancy. Four pregnant women died, and the mortality rate was 30.77% (4/13). Fetal or neonatal death up to 1 week after delivery occurred in eight (61.54%) pregnancies, and there were four cases of miscarriage, two of stillbirth, and two of neonatal death. Complications included premature birth (57.14% of neonates), small for gestational age (SGA, 7.70%), premature rupture of membranes (15.38%), and fetal stress (15.38%).

Conclusion: Early diagnosis and treatment are important for maternal survival, and corticosteroids are the first choice for most patients with HLH during pregnancy. For patients who do not respond to corticosteroids, etoposide, and termination of pregnancy may be life-saving.

Background

Hemophagocytic lymphohistiocytosis (HLH), also known as hemophagocytic syndrome, is a type of hyperinflammatory response caused by primary or secondary immune disorders. The principal clinical features of HLH are persistent fever, hepatosplenomegaly, and a decline in the number of blood cells [1]. The disease is divided into familial (primary) HLH and acquired (secondary) HLH. Primary HLH usually presents in childhood. It is caused by genetic mutation. Secondary HLH is typical in most adult HLH cases, which is secondary to infection, autoimmune diseases, and malignant tumors. As HLH becomes rapidly fatal, with mortality rates ranging between 26.5% and 74.8% [2], timely identification of suspected HLH cases and a correct diagnosis are important.

It is rare for HLH to manifest during pregnancy and most of the relevant literature involves case reports [3–6]. Given the pregnant patients' age, secondary HLH was most likely. HLH has symptoms similar to those of obstetric complications, including hemolysis, elevated liver enzymes, low platelet count (HELLP), and acute fatty liver. Additionally, because there are other causes and related factors that cooperatively induce HLH [7], diagnosing HLH in pregnancy is difficult. Clinical management of HLH also appears inconsistent across the published cases, and the effect of medications during pregnancy on the fetus needs to be considered. Thus, there is currently no consensus on the treatment of HLH during pregnancy. In the present study, we retrospectively analyzed the clinical data from 13 cases of HLH during pregnancy at our hospital and emphasized the importance of rapid diagnosis and treatment.

Results

Study population

We included 13 patients with HLH during pregnancy in this study. All the patients had singleton pregnancies, with a median gestational age of 23 weeks (range, 7–36 weeks). There was one case of HLH in the first trimester of pregnancy (7.70%), seven in the second trimester (12–28 weeks; 53.85%), and five in the third trimester (38.46%). Four (30.77%) patients were primiparas and nine (69.23%) were multiparas. There were other causes/related factors of HLH in six patients, including one with Still's disease complicated by cytomegalovirus (CMV) infection, three with systemic lupus erythematosus (SLE), 1 with SLE complicated by CMV infection, one with parvovirus B19 infection, seven with unclear causes. The patients' baseline characteristics are shown in Table 1.

Clinical symptoms and laboratory features

Fever and elevated ferritin levels were the most common symptom (13/13), followed by splenomegaly (12/13), increased fibrin or triglyceride levels (10/13), cytopenia, a diminution in two or three types of cells in peripheral blood (9/13), increased sCD25 levels (7/13), and attenuated natural killer (NK)-cell viability (3/13). The results of other tests showed that the incidence of abnormal liver function was high, with elevated liver enzymes (13/13), lactic dehydrogenase (13/13), and bilirubin levels (5/13). The copy number of CMV-DNA in two patients exceeded the normal range, and one patient was positive for parvovirus B19 (Table 1).

Therapy and outcomes

As shown in Table 1, 6 of the 13 patients (cases 1–6) were diagnosed with HLH and initiated treatment during pregnancy. They all received corticosteroids as first-line treatment, with four patients (cases 2–5) also receiving intravenous immunoglobulin [IVIG] and one (case 6) combined with etoposide. Three patients (cases 1–3) achieved partial remission (PR) and required termination of pregnancy because of the disease or stillbirth and ultimately achieved complete remission (CR). One patient (case 4) received methylprednisolone and IVIG and did not experience remission, and she continued the same treatment after vaginal delivery, achieved a PR, and was discharged from the hospital 35 days after delivery. One patient (case 6) was treated with

corticosteroids/etoposide without remission. After cesarean section, she received a regimen of dexamethasone, IVIG, etoposide, and cyclosporine A (CsA) and achieved a PR 10 days after the operation and was then discharged from the hospital. The condition of one patient (case 5) continued to deteriorate progressively despite the use of dexamethasone and IVIG, and she died of multiple organ failure the day after spontaneous abortion.

Seven patients (cases 7–13) were diagnosed with HLH after termination of pregnancy and started specific treatment thereafter. Two (cases 7–8) were treated with single corticosteroids, one patient (case 9) was treated with corticosteroids/CsA, 3 (cases 10–12) were treated with corticosteroids/etoposide, and 1 (case 13) was treated with extracorporeal membrane oxygenation (ECMO) immediately after delivery. The condition of five patients deteriorated after delivery, and three (42.9%, 3/7) died. Case 8 was treated with corticosteroids (without IVIG) 1 day after cesarean section, and the patient's condition became aggravated and she died 15 days after the operation due to multiple organ failure. The condition of case 11 worsened after cesarean section, and the patient was started on methylprednisolone treatment on the 8th day after the operation. She received dexamethasone (IVIG) and etoposide treatment on the 14th day after the operation and died 22 days after the operation due to multiple organ failure. Case 13 was admitted to the hospital with multiple organ failure, received ECMO immediately after complete curettage of the uterine cavity, and died the day after delivery. Case 7 received corticosteroids (without IVIG) treatment after cesarean section and then achieved a PR. Case 9 began treatment with hydrocortisone (with IVIG) and CsA the day after induced labor, and then achieved PR. The condition of case 10 after cesarean section deteriorated and the patient then received dexamethasone (with IVIG) and etoposide treatment, achieving a CR. Case 12 received intravenous dexamethasone on the 2nd day after spontaneous abortion and achieved a PR on the 5th day after delivery, developing a fever and showing increased triglyceride levels again on the 23rd day after delivery. This patient was then treated with a combination of etoposide and achieved a CR.

Obstetric and neonatal events

Obstetric and neonatal events are shown in Table 2. Among the 13 pregnancies, four women died (30.77%, 4/13), fetal or neonatal death up to 1 week after delivery occurred in 8 (61.54%) pregnancies. Six fetuses (46.15%) were immature (8–23 + 5 weeks); there were four miscarriages at 8–19 weeks, and two stillbirths occurred at 20 and 23 + 5 weeks. There were seven (53.85%) pregnancies that went beyond 24 weeks of gestation (26–38 weeks), and five fetuses (38.46%) survived. Cases 4 and 12 experienced PROM at weeks 29 and 26, respectively, and vaginal delivery was then performed; with these newborns dying on the 3rd day and the same day after birth, respectively. The most common obstetric complication was premature delivery (57.14% of neonates), followed by SGA (7.70%, 1/13).

Discussion

In our study, the most common time of onset for HLH in pregnancy was in the second trimester of pregnancy, followed by the third trimester, which is similar to the previous studies (Table 3). Our hypothesis for these phenomena is that pregnancy may be a regulatory immune state, immunologic alterations with advancing pregnancy impair the clearance of pathogens, resulting in an increased frequency of disease caused by some pathogens [8, 9].

There is currently no guideline for HLH during pregnancy. Treatments are mostly selected on clinical experience and clinical manifestations. In general, the treatment of HLH includes inhibition of life-threatening inflammatory responses using immunosuppressive agents and cytotoxic drugs, treatment of the underlying cause, or both. As for the causes of HLH in pregnancy, among the 13 patients in this study, 5 had autoimmune diseases, 1 with parvovirus B19 infection, and 7 with unclear causes. The prognosis is variable with different underlying diseases. We found that patients with autoimmune diseases and viral infections have good outcomes and the patients for whom causes were not known had worse outcomes with respect to maternal health.

The widely used standard treatment schemes at present are HLH-1994 [1] and HLH-2004 [32]. Medications should be carefully considered. Corticosteroids are part of the HLH-1994 and HLH-2004 regimens—reducing immune system activity and inhibiting the inflammatory response—and are classified as category C drugs by the U.S. Food and Drug Administration (FDA). During pregnancy, especially after the first trimester, women taking corticosteroids have a relatively low risk of birth defects. Regardless of the precipitating cause, corticosteroids are the first choice for most pregnant patients with HLH. In previous reports, 38 (95%, 38/40) women were treated with corticosteroids as the initial treatment, and 12 (31.6%, 12/38) manifested a curative effect. Of the 13 patients with HLH in this study, 12 (92.3%, 12/13) were treated with corticosteroids and 5 (41.7%, 5/12) showed a curative effect.

The Topo II inhibitor etoposide is one of the essential drugs in HLH-94 and HLH-04 regimens. Prognostic factors of adult hemophagocytic syndrome indicated that the use of etoposide as the first-line treatment tended to be associated with a better outcome [33]. Etoposide is a cell cycle-specific antitumor drug that is classified as category D by the FDA. Etoposide is commonly used in the treatment of ovarian cancers, and it is considered safe for the fetus if given during the second or third trimester. No neonatal malformations have been reported [34]. Song et al. [27] reported the use of etoposide in a pregnant patient with HLH. No congenital malformations were found in the fetus. However, in a study performed in mice, etoposide had adverse effects on fetal ovarian development. Exposure of pre-follicular ovaries to etoposide resulted in a near-complete elimination of germ cells prior to follicle formation [35]. In the current study, four patients were treated with etoposide, of whom one was treated during pregnancy, and we observed no abnormalities in the neonates. Our other three patients were treated after delivery, and two achieved CR, while one died of multiple organ failure 22 days after delivery. The number of cases of etoposide application during pregnancy was small; the timing, dose and frequency of the drug—as well as the effect of the drug on the fetus—still require further investigation.

CsA may be an effective treatment for patients with HLH who do not show a response to corticosteroids [31]. In our study, two patients were treated with CsA, including one with the combination of hydrocortisone and CsA, and one with the combination of dexamethasone, etoposide, and CsA. The FDA classifies CsA as class C drug for pregnancy. CsA can inactively cross the placenta and enter the fetal circulation [36]. A systematic review suggested that use of CsA during pregnancy is associated with premature delivery and low birth weight, but it is difficult to determine if any risks associated with CsA therapy during pregnancy are due to drug exposure alone or to pre-existing maternal comorbidities [37].

Patients with HLH in pregnancy can go into remission after termination of pregnancy. Teng et al. [3] hypothesized that the pathogenesis of HLH during pregnancy was similar to preeclampsia, where the immature placenta releases genetically foreign material into the maternal circulation. Maternal T-lymphocytes (which are unable to recognize unfamiliar human lymphocyte antigens), may then trigger a systemic inflammatory response and cytokine storm. Termination of pregnancy may thus prevent the maternal condition from continuing to deteriorate and allow for timely chemotherapy. In previous studies, six patients (40%, 6/15 from a total of 40 cases) attained remission after termination of pregnancy [3–5, 11, 15, 27], including four with unclear causes, one complicated by SLE, and one complicated by autoimmune hemolytic anemia. In our study, termination of pregnancy was effective in two patients. However, the condition of six cases was exacerbated or did not improve after termination of pregnancy. The overall effect of termination of pregnancy is still controversial in HLH. The relationship between pregnancy and HLH requires further elucidation. If corticosteroid treatment is ineffective, termination of pregnancy may be an effective method of treatment.

There are inherent biases to our study because it was a retrospective study conducted in a referral center. The majority of patients worsen at the local hospitals. Therefore, this may have generated bias in the evaluation of treatment effects. Additionally, the details of most neonatal outcomes were relatively unclear. Therefore, it is important to perform more investigations to develop a standard treatment protocol for HLH in pregnancy.

Conclusions

In summary, the specific mechanisms underlying HLH during pregnancy are unclear. Although several associated factors have been investigated, the etiology of many cases remained unclear. Corticosteroids are the first choice for most patients with HLH during pregnancy, causes and related factors need to be identified and treated accordingly. Etoposide and termination of pregnancy may then be effective for patients with ineffective corticosteroid treatment. For patients after delivery—especially for severe patients—etoposide may be used as soon as possible to improve the prognosis. Our conclusions, however, still need to be further confirmed using a larger sample size.

Methods

This study method was approved by the Peking Union Medical College Hospital Review Board (reference number: S-K1161). The need for written informed consent was waived because of the retrospective nature of the study, and the data set was deidentified in order to protect patient privacy. Using a computerized database at the Peking Union Medical College Hospital in China, the patients with HLH in pregnancy from January 2000 to December 2019 were identified retrospectively.

In our study, the time of onset for HLH coincided with the development of pregnancy. The patient had no significant past medical or family history of HLH, and no patient conducted a molecular diagnosis. The diagnosis of HLH is based on five out of the following eight criteria according to the HLH-2004 trial [32]: (1) fever; (2) splenomegaly; (3) cytopenia (affecting ≥ 2 of 3 lineages in peripheral blood), with hemoglobin levels <90 g/L, platelet count $<100 \times 10^9$ /L, and neutrophil count $<1.0 \times 10^9$ /L; (4) hypertriglyceridemia and/or hypofibrinogenemia, with fasting triglyceride levels ≥ 3.0 mmol/L and fibrinogen levels ≤ 1.5 g/L; (5) hemophagocytosis in the bone marrow, spleen, or lymph nodes, and no evidence of malignancy; (6) low or absent NK-cell activity (according to the local laboratory reference); (7) ferritin levels ≥ 500 μ g/L; and (8) soluble CD25 (i.e., soluble interleukin-2 receptor) levels $\geq 2,400$ U/mL.

Etiologies of and factors related to HLH including rheumatologic, infectious, and oncologic workups were recorded for diagnostic and prognostic purposes. HLH-related laboratory indices that were recorded included routine blood results, liver function, serum ferritin levels, fibrinogen levels, triglyceride levels, hemophagocytosis, NK-cell viability, soluble CD25 levels. The presenting signs and symptoms, treatment, and outcome of HLH during pregnancy were also recorded.

We collected maternal characteristics including age, gravidity, parity, gestational age at disease onset, maternal outcomes, gynecological and obstetric history, major medical history, and major family history. The perinatal outcomes included preterm labor (delivery after 24 and before 37 full weeks of gestation), SGA (birth weight $<$ the 10th percentile), preeclampsia, eclampsia, HELLP, PROM, gestational age, method of terminating pregnancy, birthweight, Apgar score, miscarriage (spontaneous fetal loss before 20 weeks of gestation), stillbirth, and neonatal death. The term “stillbirth” was used to describe fetal deaths at 20 weeks of gestation or later. Neonatal death was defined as the death of an infant between 0 and 7 days after birth.

Descriptive statistics—such as frequency, percentage, and range—were used for presentation of variables. The distribution of age and gestation is shown as medians and interquartile ranges. Differences between groups were assessed using the Student's *t*-test. Categorical variables, including clinical characteristics and complications, are expressed as proportions and were compared using the Chi-square test or Fisher's exact-probability test. All statistical analyses were performed using SPSS (version 25.0, Chicago, IL, USA), with an alpha of 0.05 used as the cutoff for significance.

Abbreviations

HLH: hemophagocytic lymphohistiocytosis; HELLP: hemolysis, elevated liver enzymes, low platelet count; NK-cell: natural killer –cell; CsA: cyclosporine A; NA: information not available; SLE: systemic lupus erythematosus; Hb: hemoglobin; WBC: white blood cell count; Plt: platelet count; ALT: alanine transaminase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; TG: triglycerides; IVIG: intravenous immunoglobulin; PROM: premature rupture of the membranes; SGA: small for gestational age; VD: vaginal delivery; CS: cesarean section; Fbg: fibrinogen; AIHA: autoimmune hemolytic anemia; CMV: cytomegalovirus; EBV: Epstein–Barr virus; HSV: herpes simplex virus; IUGR: intrauterine growth retardation; CR: complete remission; PR: partial remission; BMT: bone marrow transplantation; R-CHOP: rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; ECHOP: etoposide/cyclophosphamide/doxorubicin/vincristine/prednisone; allo-HSCT: allogeneic hematopoietic stem cell transplant; FDA: Food and Drug Administration

Declarations

Ethics approval and consent to participate

This study method was approved by the Peking Union Medical College Hospital Review Board (reference number: S-K1161). The need for written informed consent was waived because of the retrospective nature of the study, and the data set was deidentified in order to protect patient privacy. Our study was done in compliance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to patient data safety restrictions but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the National Key R & D Program of China (No. 2019YFC1005100).

Authors' contributions

CL and JL substantially contributed to the study concept and design; the acquisition, analysis, and interpretation of the data; and the writing of the manuscript. JG and CL contributed to the understanding of data and performed critical revisions of relevant intellectual content. All authors approved publication of the final version.

Acknowledgements

We thank all of our patients for agreeing to participate in this study.

References

1. Henter JI, Aricò M, Egeler RM, Elinder G, Favara BE, Filipovich AH, et al. HLH-94: a treatment protocol for hemophagocytic lymphohistiocytosis. *Med Pediatr Oncol.* 1997;28:342–7. doi:10.1002/(SICI)1096-911X(199705)28:5<342::AID-MPO3>3.0.CO;2-H.
2. Yildiz H, Van Den Neste E, Defour JP, Danse E, Yombi JC. Adult haemophagocytic lymphohistiocytosis: a review. *QJM.* 2020; doi:10.1093/qjmed/hcaa011.
3. Teng CL, Hwang GY, Lee BJ, Wang RC, Chou MM. Pregnancy-induced hemophagocytic lymphohistiocytosis combined with autoimmune hemolytic anemia. *J Chin Med Assoc.* 2009;72:156–9. doi:10.1016/S1726-4901(09)70043-7.
4. Cheng J, Niu J, Wang Y, Wang C, Zhou Q, Chen Y, et al. Hemophagocytic lymphohistiocytosis in pregnancy: a case report and review of the literature. *J Obstet Gynaecol.* 2019;40:153–9. doi:10.1080/01443615.2019.1601168.
5. Shukla A, Kaur A, Hira HS. Pregnancy induced haemophagocytic syndrome. *J Obstet Gynaecol India.* 2013;63:203–5. doi:10.1007/s13224-011-0073-0.
6. He M, Jia J, Zhang J, Beejadhursing R, Sharifu LM, Yu J, et al. Pregnancy-associated hemophagocytic lymphohistiocytosis secondary to NK/T cells lymphoma: A case report and literature review. *Medicine (Baltimore).* 2017;96:e8628. doi:10.1097/MD.0000000000008628.
7. Chmait RH, Meimin DL, Koo CH, Huffaker J. Hemophagocytic syndrome in pregnancy. *Obstet Gynecol.* 2000;95:1022–4. doi:10.1016/S0029-7844(00)00834-6.
8. Pazos M, Sperling RS, Moran TM, Kraus TA. The influence of pregnancy on systemic immunity. *Immunol Res.* 2012;54:254–61. doi:10.1007/s12026-012-8303-9.
9. Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. *N Engl J Med.* 2014;370:2211–8. doi:10.1056/NEJMr1213566.

10. Dunn T, Cho M, Medeiros B, Logan A, Ungewickell A, Liedtke M. Hemophagocytic lymphohistiocytosis in pregnancy: a case report and review of treatment options. *Hematology*. 2012;17:325–8. doi:10.1179/1607845412Y.0000000007.
11. Pérard L, Costedoat-Chalumeau N, Limal N, Hot A, Cohen J, Vauthier-Brouzes D, et al. Hemophagocytic syndrome in a pregnant patient with systemic lupus erythematosus, complicated with preeclampsia and cerebral hemorrhage. *Ann Hematol*. 2007;86:541–4. doi:10.1007/s00277-007-0277-7.
12. Nakabayashi M, Adachi T, Izuchi S, Sugisaki A. Association of hypercytokinemia in the development of severe preeclampsia in a case of hemophagocytic syndrom. *Semin Thromb Hemost*. 1999;25:467–71. doi:10.1055/s-2007-994952.
13. Mihara H, Kato Y, Tokura Y, Hattori Y, Sato A, Kobayashi H, et al. Epstein-Barr virus-associated hemophagocytic syndrome during mid-term pregnancy successfully treated with combined methylprednisolone and intravenous immunoglobulin. *Rinsho Ketsueki*. 1999;40:1258–64.
14. Hanaoka M, Tsukimori K, Hojo S, Abe Y, Mutou T, Muta K, et al. B-cell lymphoma during pregnancy associated with hemophagocytic syndrome and placental involvement. *Clin Lymphoma Myeloma*. 2007;7:486–90. doi:10.3816/CLM.2007.n.033.
15. Chien CT, Lee FJ, Luk HN, Wu CC. Anesthetic management for cesarean delivery in a parturient with exacerbated hemophagocytic syndrome. *Int J Obstet Anesth*. 2009;18:413–6. doi:10.1016/j.ijoa.2009.02.016.
16. Klein S, Schmidt C, La Rosée P, Pletz M, Harz S, Dirsch O, et al. Fulminant gastrointestinal bleeding caused by EBV-triggered hemophagocytic lymphohistiocytosis: report of a case. *Z Gastroenterol*. 2014;52:354–9. doi:10.1055/s-0034-1366154.
17. Goulding EA, Barnden KR. Disseminated herpes simplex virus manifesting as pyrexia and cervicitis and leading to reactive hemophagocytic syndrome in pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 2014;180:198–9. doi:10.1016/j.ejogrb.2014.05.005.
18. Mayama M, Yoshihara M, Kokabu T, Oguchi H. Hemophagocytic lymphohistiocytosis associated with a parvovirus B19 infection during pregnancy. *Obstet Gynecol*. 2014;124:438–41. doi:10.1097/aog.0000000000000385.
19. Tumian NR, Wong CL. Pregnancy-related hemophagocytic lymphohistiocytosis associated with cytomegalovirus infection: a diagnostic and therapeutic challenge. *Taiwan J Obstet Gynecol*. 2015;54:432–7. doi:10.1016/j.tjog.2014.11.023.
20. Bachar Samra MY, Arnaout S, Azzi J. Idiopathic hemophagocytic lymphohistiocytosis during pregnancy treated with steroids. *Hematol Rep*. 2015;7:6100. doi:10.4081/hr.2015.6100.
21. Giard JM, Decker KA, Lai JC, Gill RM, Logan AC, Fix OK. Acute liver failure secondary to hemophagocytic lymphohistiocytosis during pregnancy. *ACG Case Rep J* 2006;3:e612. doi:10.14309/crj.2016.135.
22. Fernández AA, de Velasco Pérez DF, Fournier MCJ, del Prado JM, Torras BP, Palomo MC. Hemophagocytic syndrome secondary to tuberculosis at 24-week gestation. *Int J Mycobacteriol*. 2014;6:108–10. doi:10.4103/ijmy.ijmy_14_17.
23. Takada H, Kimura N, Yoshihashi-Nakazato Y, Kawahata K, Kohsaka H. Discoid lupus erythematosus complicated with pregnancy-induced hemophagocytic syndrome. *Intern Med*. 2017;56:1581–3. doi:10.2169/internalmedicine.56.8156.
24. Rousselin A, Alavi Z, Le Moigne E, Renard S, Tremouilhac C, Delluc A, et al. Hemophagocytic syndrome in pregnancy: case report, diagnosis, treatment, and prognosis. *Clin Case Rep*. 2017;5:1756–64. doi:10.1002/ccr3.1172.
25. Yildiz H, Vandercam B, Thissen X, Komuta M, Lanthier N, Debieve F, et al. Hepatitis during pregnancy: a case of hemophagocytic lymphohistiocytosis. *Clin Res Hepatol Gastroenterol*. 2018;42:e49–55. doi:10.1016/j.clinre.2017.10.007.
26. Sarkissian S, Khan Y, Farrell D, Constable D, Brem E. Hemophagocytic lymphohistiocytosis in the setting of HELLP syndrome. *Clin Case Rep* 2018;6:2466–70. doi:10.1002/ccr3.1828.
27. Song Y, Wang Z, Hao Z, Li L, Lu J, Kang H, et al. Requirement for etoposide in the treatment of pregnancy related hemophagocytic lymphohistiocytosis: a multicenter retrospective study. *Orphanet J Rare Dis*. 2019;14:50. doi:10.1186/s13023-019-1033-5.
28. Parrott J, Shilling A, Male HJ, Holland M, Clark-Ganheart CA. Hemophagocytic Lymphohistiocytosis in Pregnancy: a case series and review of the current literature. *Case Rep Obstet Gynecol*. 2019;2019:9695367. doi:10.1155/2019/9695367.
29. Nasser MF, Sharma S, Albers E, Sharma S, Duggal A. Pregnancy-related hemophagocytic lymphohistiocytosis associated with herpes simplex virus-2 infection: a diagnostic dilemma. *Cureus*. 2018;10:e2352. doi:10.7759/cureus.2352.
30. Kerley RN, Kelly RM, Cahill MR, Kenny LC. Haemophagocytic lymphohistiocytosis presenting as HELLP syndrome: a diagnostic and therapeutic challenge. *BMJ Case Rep*. 2017;2017. doi:10.1136/bcr-2017-219516.
31. Yamaguchi K, Yamamoto A, Hisano M, Natori M, Murashima A. Herpes simplex virus 2-associated hemophagocytic lymphohistiocytosis in a pregnant patient. *Obstet Gynecol*. 2005;105:1241–4. doi:10.1097/01.AOG.0000157757.54948.9b.
32. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48:124–31. doi:10.1002/pbc.21039.
33. Arca M, Fardet L, Galicier L, Riviére S, Marzac C, Aumont C, et al. Prognostic factors of early death in a cohort of 162 adult haemophagocytic syndrome: impact of triggering disease and early treatment with etoposide. *Br J Haematol*. 2015;168:63–8. doi:10.1111/bjh.13102.
34. Karimi Z M, Behtash N, Modares G M. Good pregnancy outcome after prenatal exposure to bleomycin, etoposide and cisplatin for ovarian immature teratoma: a case report and literature review. *Arch Gynecol Obstet*. 2008;277:75-8. doi:10.1007/s00404-007-0416-3.
35. Stefansdottir A, Johnston Z C, Powles-Glover N, Anderson, R A, Adams, I R, Spears, N. Etoposide damages female germ cells in the developing ovary. *BMC Cancer*. 2016;16:482. doi:10.1186/s12885-016-2505-9.
36. Tendron A, Gouyon J B, Decramer S. In utero exposure to immunosuppressive drugs: experimental and clinical studies. *Pediatr Nephrol*. 2002;17:121-30. doi:10.1007/s00467-001-0776-z.
37. Paziana K, Del M M, Cardonick E, Moritz M, Keller M, Smith B, et al. Ciclosporin use during pregnancy. *Drug Saf*. 2013;36:279-94. doi:10.1007/s40264-013-0034-x.

Tables

Table 1 Characteristics of patients with HLH during pregnancy

Case	Age (years)	Cause/associated diagnoses		Fever	Splenomegaly	WBC (10 ⁹ /L)	Hb (g/L)	Plt (10 ⁹ /L)	Fbg (g/L)	ALT/AST (U/L)	LDH (U/L)
1	30	Unknown		+	+	2.06	76	40	3.95	119/210	983
2	24	Still's disease/CMV		+	+	2.82	79	35	1.1	930/NA	304
3	23	SLE		+	+	1.31	84	69	2.79	86/164	515
4	22	SLE/CMV		+	+	10.3	66	1	0.86	304/531	1037
5	30	Unknown		+	+	0.74	53	9	1	931/2674	5800
6	24	Unknown		+	+	0.31	73	77	0.66	138/293	1071
7	28	Parvovirus B19		+	+	0.83	55	31	0.54	260/805	2874
8	33	Unknown		+	+	15.17	99	46	0.66	1114/712	6410
9	31	SLE		+	+	0.6	76	76	1.95	582/397	1637
10	27	SLE		+	+	1.93	83	290	0.65	161/332	1163
11	29	Unknown		+	+	9.63	99	33	0.47	144/194	2973
12	23	Unknown		+	+	14.18	71	38	0.5	112/452	1651
13	31	Unknown		+	–	3.38	119	57	1.29	268/351	5584
Case	G/P	Gestational age at presentation (weeks)	Timing of diagnosis and treatment	Corticosteroids		IVIg	Etoposide	Cyclosporine	Complications		Gestation (weeks), Del method
1	G2P1	16	Prepartum	+		–	–	–	Stillbirth		20, CS
2	G1P0	13	Prepartum	+		+	–	–	Miscarriage		19, CS
3	G1P0	12	Prepartum	+		+	–	–	Miscarriage		19, medical abortion
4	G1P0	24	Prepartum	+		+	–	–	PROM, preterm labor		29, VD
5	G2P1	19	Prepartum	+		+	–	–	Stillbirth		23 + 5, VD
6	G2P1	28	Prepartum	+		+	+	+	SGA		31, CS
7	G2P2	36	Postpartum	+		–	–	–			37, CS
8	G3P2	32	Postpartum	+		–	–	–	Preterm labor		36, CS
9	G3P0	14	Postpartum	+		+	–	+	Miscarriage		18, medical abortion
10	G2P1	36	Postpartum	+		+	+	–			38, CS
11	G3P2	35	Postpartum	+		+	+	–			37, CS
12	G2P1	23	Postpartum	+		–	+	–	PROM		26, VD
13	G3P1	7	Postpartum	–		+	–	–	Miscarriage		8, curettage

NA information not available, CMV cytomegalovirus, SLE systemic lupus erythematosus, Hb hemoglobin (g/L), WBC white blood cell count (10⁹/L), Plt platelet count (10⁹/L), ALT alanine transaminase, AST aspartate aminotransferase, LDH lactate dehydrogenase, TG triglycerides (μmol/L), IVIG intravenous immunoglobulin, PROM premature rupture of the membranes, SGA small for gestational age, VD vaginal delivery, CS cesarean section, Fbg fibrinogen

Table 2 Obstetric and neonatal events

Complications	<i>N</i>	%
Maternal outcome		
Maternal death	4	30.77
Mode of delivery		
Vaginal	6	46.15
Cesarean section	7	53.85
Fetal or neonatal outcome		
Live births	5	38.46
Premature delivery (<37 weeks)	4	57.14
PROM	2	15.38
SGA	1	7.70
Fetal or neonatal death	8	61.54
Miscarriage <20 weeks	4	30.77
Stillbirth ≥20 weeks	2	15.38
Neonatal mortality <1 week	2	15.38

PROM premature rupture of the membranes, *SGA* small for gestational age

Table 3 Characteristics of patients previously reported with HLH during pregnancy

Case	Age (years)	Cause/associated diagnoses	Treatment and outcome	Period of gestation (weeks)	Complications	Gestation (week), delivery method	Indication	Birth weight (g)
Chmait et al. [7]	24	Necrotizing lymphadenitis	IVIg postpartum day 6	29	SGA	30, CS	Condition worsened, breech presentation	1100
Teng et al. [3]	28	AIHA	Steroids failed, remission after CS	23	SGA	29, CS	Fetal distress	740
Dunn et al. [10]	41	Still's disease	Remission with corticosteroids	19	SGA	30, CS	IUGR	
Pérard et al. [11]	28	SLE	Failed with corticosteroids/IVIg, remission after delivery and third IVIg dose	22	Eclampsia, cerebral hemorrhage	30, VD	PPROM	1420
Nakabayashi et al. [12]	30	Unknown	Failed with IVIg, remission with antithrombin concentrate	21	Preeclampsia, SGA	29, CS	Preeclampsia, IUGR, Fetal distress	727
Mihara et al. [13]	32	EBV	Failed with corticosteroids, remission with IVIg acyclovir, methylprednisolone	16		35, VD		NA
Hanaoka et al. [14]	33	B-cell lymphoma	Failed with corticosteroids, remission with R-CHOP postpartum day 8	21		28, CS	Fetal distress	
Chien et al. [15]	28	Unknown	Failed with corticosteroids, remission after CS	23	SGA	30, CS	Fetal distress	740
Klein et al. [16]	39	EBV	Failed with steroids, CsA, etoposide, rituximab	30		31, CS	Twins, gastrointestinal bleeding	
Goulding and Barnden [17]	27	HSV	Remission with steroids, acyclovir	23+5		24, CS	PPROM and chorioamnionitis	
Mayama et al. [18]	28	Parvovirus B19	Remission with steroids	20		37, VD		2870
Tumian and Wong [19]	35	CMV	Failed with steroids, IVIg, CsA, acyclovir, plasma exchange	38		38, CS	Fetal distress, previous C	
Bachar Samra et al. [20]	36	Unknown	Remission with steroids	16		Term, VD		
Giard et al. [21]	35	KF lymphadenitis	Failed with steroids and etoposide	20		22, spontaneous abortion		
Fernández et al. [22]	20	Tuberculosis	Failed with steroids IVIg, etoposide, CsA. Remission after anti-tuberculosis treatment	24	PPROM	29, CS	Breech presentation, PPRM	1140
Takada et al. [23]	35	SLE	Remission with steroids	11		35, VD		
Rousselin et al. [24]	44	Raynaud syndrome	Remission with steroids	30	SGA	38, VD	IUGR Oligohydramnios	
Yildiz et al. [25]	36	Unknown	Remission with steroids	29		31 + 6, CS	Fetal distress	
He et al. [6]	27	NK/T-cell lymphoma	Failed with steroids and etoposide	30		30 + 4, CS	Fetal distress	
Sarkissian et al. [26]	30	HSV-1, CMV, EBV	Failed with steroids and etoposide	35 + 2	HELLP	35 + 2, CS	HELLP	
Song et al. [27]	26	Infection (<i>Staphylococcus epidermidis</i>)	Failed with corticosteroids, IVIg. Remission with etoposide	31		31, VD		
Song et al.	36	Unknown	Remission with	14		Spontaneous miscarriage		

[27]			corticosteroids, etoposide					
Song et al. [27]	30	Angioimmunoblastic T-cell lymphoma	Failed with steroids and etoposide. Remission after ECHOP, allo-HSCT	34		34, VD		
Song et al. [27]	30	Unknown	Failed with corticosteroids/delivery, remission with HLH-04 regimen, DEP regimen	30		35, CS		
Song et al. [27]	27	EBV	Failed with steroids, remission with etoposide	19		NA		
Song et al. [27]	29	Unknown	Failed with corticosteroids/delivery, remission with etoposide	30		30, CS	Transverse position	
Song et al. [27]	24	Still's disease	Remission with corticosteroids, fludarabine	10		16, Induced abortion		
Song et al. [27]	24	Unknown	Failed with corticosteroids and cyclosporine, remission after abortion	17		19, Induced abortion		
Song et al. [27]	26	Tuberculosis	Failed with corticosteroid, remission after anti-tuberculosis treatment	28		28, VD		
Song et al. [27]	20	SLE	Remission with corticosteroids and cyclosporine.	10		Spontaneous miscarriage		
Song et al. [27]	24	Unknown	Remission with corticosteroids	36		36, VD		
Song et al. [27]	29	Unknown	Failed with corticosteroids/delivery	28		28, VD		
Song et al. [27]	25	EBV	Failed with corticosteroids/delivery	24		24, Delivered		
Parrott et al. [28]	28	SLE	Failed with steroids IVIG and etoposide	18	SGA	21+4, Spontaneously delivered	IUGR	
Parrott et al. [28]	37	CMV	Remission with steroids, etoposide, acyclovir, HLH-94	24	SGA	37, VD	IUGR	130%
Cheng et al. [4]	29	Unknown	Failed with steroids, remission with etoposide, corticosteroid IVIG after CS	26 + 2		27+2, CS	Condition worsened	100%
Nasser et al. [29]	36	HSV 2	Remission with steroids, acyclovir	31		31, CS	Preeclampsia?	226%
Shukla et al. [5]	23	Unknown	Failed with steroids, remission after abortion	10		Spontaneous abortion		
Kerley et al. [30]	33	Unknown	Failed with steroids. BMT, CR	22		22, VD (induced labor)		
Yamaguchi et al. [31]	NA	HSV 2	Failed with steroids, remission with cyclosporine, acyclovir	Midgestation		37, CS	Breech presentation	259%

NA information not available, HLH hemophagocytic lymphohistiocytosis, AIHA autoimmune hemolytic anemia, SLE systemic lupus erythematosus, CMV cytomegalovirus, EBV Epstein–Barr virus, HSV herpes simplex virus, IVIG intravenous immunoglobulin, R-CHOP rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone, ECHOP etoposide/cyclophosphamide/doxorubicin/vincristine/prednisone, VD vaginal delivery, CS cesarean section, BMT bone marrow transplantation, allo-HSCT allogenic hematopoietic stem cell transplant, CsA cyclosporine A, PPRM

premature rupture of the membranes, *NK* natural killer, *SGA* small for gestational age, *HELLP* hemolysis, elevated liver enzymes, low platelet count, *IUGR* intrauterine growth retardation, *CR* complete remission, *PR* partial remission