Management of hemophagocytic lymphohistiocytosis in pregnancy: Case series study and literature review

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Abstract

Aim: The diagnosis and treatment of hemophagocytic lymphohistiocytosis (HLH) in pregnancy is challenging due to its rarity. 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). Twelve patients received corticosteroids, and four patients (with/without intravenous immunoglobulin) showed a curative effect. Two patients who were treated with dexamethasone and etoposide after termination of pregnancy achieved complete remission. Two patients attained remission after termination of pregnancy. Four pregnant women died, and the mortality rate was 30.8% (4/13). Fetal or neonatal death up to 1 week after delivery occurred in eight (61.5%) pregnancies.

Conclusions: 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.

Key words: etoposide, hemophagocytic lymphohistiocytosis, pregnancy, steroids, therapeutics.

Introduction

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. Given the pregnant patients’ age, secondary HLH was most likely. 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 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, 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. 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.

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 dataset was de-identified in order to protect patient privacy. Our study was done in compliance with the Declaration of Helsinki. 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.

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, small for gestational age (SGA), preeclampsia, eclampsia, HELLP, premature rupture of the membranes, method of terminating pregnancy, gestational age, birthweight, Apgar score, miscarriage, 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.

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: (1) fever; (2) splenomegaly; (3) cytopenia (affecting ≥2 of 3 lineages in peripheral blood), with hemoglobin levels <90 g/L, platelet count <100 × 10⁹/L, and neutrophil count <1.0 × 10⁹/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 μg/L; and (8) soluble CD25 (i.e., soluble interleukin-2 receptor) levels ≥2400 U/ml. We also calculated the HScore of all the patients to estimate the probability of HLH.

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

Descriptive statistics—such as frequency, percentage, and range—were used for the 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), with an alpha of 0.05 used as the cutoff for significance.

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 (7.7%), seven in the second trimester (53.8%), and five in the third trimester (38.5%). Four (30.8%) patients were primiparas and nine (69.2%) were multiparas. There were related factors of HLH in six patients, including one with Still’s disease complicated by cytomegalovirus (CMV) infection, three with systemic lupus erythematosus (SLE), one with SLE complicated by CMV infection, one with parvovirus B19 infection, and seven with unclear causes. The patients’ characteristics are shown in Table 1.
### TABLE 1 Characteristics of patients with HLH during pregnancy

| Case | Age (years) | G/P | Associated diagnoses | Fever | Splenomegaly | WBC (10^9/L) | Hb (g/L) | Plt (10^9/L) | Fbg (g/L) | ALT/AST (U/L) | Ferritin (ng/mL) | Triglycerides (mmol/L) | sCD25 (pg/mL) | NK-cell activity | Bone marrow BX | HScore, probability of HLH (%)<sup>a</sup> |
|------|-------------|-----|----------------------|-------|---------------|--------------|-----------|-------------|-----------|---------------|----------------|-------------------|----------------|-----------------|---------------|-------------------------------|
| 1    | 30          | G2P1| Pregnancy            | +     | +             | 2.06         | 76        | 40          | 3.95      | 119/210       | 1900            | 3.06              | NA              | NA              | NA            | +                           | 219, 96.04%     |
| 2    | 24          | G1P0| Still's disease/CMV  | +     | +             | 2.82         | 79        | 35          | 1.1       | 930/NA        | 8584            | NA                | NA              | NA              | NA            | +                           | 275, 99.98%     |
| 3    | 23          | G1P0| SLE                  | +     | +             | 1.31         | 84        | 69          | 2.79      | 86/164        | 690             | 2.24              | 18/106          | NA              | NA            | +                           | 272, 99.85%     |
| 4    | 22          | G1P0| SLE/CMV              | +     | +             | 1.03         | 66        | 1           | 0.86      | 304/331       | 31/461          | 15               | 31/161          | 17              | -             | 232, 99.96%    |
| 5    | 30          | G2P1| Unknown              | +     | +             | 0.74         | 53        | 9           | 1         | 931/2674      | 68/900          | 4.37              | NA              | NA              | NA            | +                           | 319, 99.99%     |
| 6    | 24          | G2P1| Pregnancy            | +     | +             | 0.31         | 73        | 77          | 0.66      | 136/2921      | 26/950          | 6.42              | NA              | NA              | NA            | +                           | 319, 99.99%     |
| 7    | 28          | G2P2| Parvovirus           | +     | +             | 0.83         | 55        | 31          | 0.54      | 260/865       | 31/725          | 4.05              | NA              | NA              | NA            | -                           | 302, 99.98%     |
| 8    | 33          | G3P2| Unknown              | +     | +             | 15.17        | 99        | 46          | 0.66      | 1144/712      | 12799            | 6.35              | 15/811          | 159              | -             | 270, 99.81%    |
| 9    | 31          | G3P0| SLE                  | +     | +             | 0.6          | 76        | 76          | 1.95      | 582/397       | 22850           | 1.13              | 29/30           | 141              | +             | 236, 99.63%    |
| 10   | 27          | G2P1| SLE                  | +     | +             | 1.93         | 83        | 290         | 0.65      | 161/332       | 1896             | 33.56             | 82/20           | 9.32             | -             | 232, 99.96%    |
| 11   | 29          | G3P2| Unknown              | +     | +             | 9.63         | 99        | 33          | 0.47      | 144/194       | 66215           | 15.14             | 18/8500.8       | NA              | +             | 285, 99.93%    |
| 12   | 23          | G2P1| Unknown              | +     | +             | 14.18        | 71        | 38          | 0.5       | 112/452       | 41756           | 15.17             | 28/312          | 14118            | +             | 309, 99.98%    |
| 13   | 31          | G3P1| Unknown              | +     | -             | 3.38         | 139       | 57          | 1.29      | 268/351       | 6950            | 12.6              | NA              | NA              | NA            | +                           | 236, 98.95%     |

Abbreviations: ALT, alanine transaminase (normal range, 5–40 U/L); AST, aspartate aminotransferase (normal range, 5–37 U/L); BX, biopsy; CMV, cytomegalovirus; Fbg, fibrinogen (normal range, 1.8–3.5 g/L); Ferritin (normal range, 14–307 ng/ml); Hb, hemoglobin (normal range, 110–150 g/L); HLH, hemophagocytic lymphohistiocytosis; NK-cell activity (normal range, ≥15.11%); NA, information not available; Plt, platelet count (normal range, 100–300 × 10<sup>9</sup>/L); SLE, systemic lupus erythematosus; sCD25, soluble interleukin-2 receptor (normal range, <6400 pg/ml); Triglyceride (normal range, 0.45–1.70 mmol/L); VD, vaginal delivery; WBC, white blood cell count (normal range, 4–10 × 10<sup>9</sup>/L), and

*Probability of HLH is estimated according to the HScore.
Therapy and outcomes

As shown in Table 2, 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. 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 the termination of pregnancy and started specific treatment thereafter. Case 7 received corticosteroids (without IVIG) treatment after cesarean section and then achieved a PR. Case 9 began treatment

| Case | Timing of diagnosis and treatment | Treatment and outcome | Complications | Gestation (weeks), delivery method | Maternal/ fetal survival |
|------|----------------------------------|-----------------------|---------------|-----------------------------------|-------------------------|
| 1    | Prepartum                        | Corticosteroids       | Stillbirth    | 20, CS                            | Yes/yes                 |
| 2    | Prepartum                        | Corticosteroids, IVIG | Miscarriage   | 19, CS                            | Yes/no                  |
| 3    | Prepartum                        | Corticosteroids, IVIG | Miscarriage   | 19, medical abortion              | Yes/no                  |
| 4    | Prepartum                        | Methylprednisolone and IVIG treatment failed, remission with methylprednisolone and IVIG after delivery | PROM, preterm labor | 29, VD | Yes/no |
| 5    | Prepartum                        | Dexamethasone and IVIG treatment failed | Stillbirth | 23 + 5, VD | No/no |
| 6    | Prepartum                        | Corticosteroids and etoposide treatment failed, remission with dexamethasone, IVIG, etoposide, and cyclosporine after cesarean section | SGA | 31, CS | Yes/yes |
| 7    | Postpartum                       | Remission with corticosteroids |          | 37, CS                            | Yes/yes                 |
| 8    | Postpartum                       | Corticosteroid treatment failed | Preterm labor | 36, CS | Yes/no |
| 9    | Postpartum                       | Remission with corticosteroids, IVIG, cyclosporine | Miscarriage | 18, medical abortion | Yes/no |
| 10   | Postpartum                       | Remission with dexamethasone, IVIG, etoposide |          | 38, CS                            | Yes/yes                 |
| 11   | Postpartum                       | Methylprednisolone, IVIG, and etoposide treatment failed |          | 37, CS                            | No/yes                  |
| 12   | Postpartum                       | Dexamethasone treatment failed, remission with dexamethasone and etoposide | PROM | 26, VD | Yes/no |
| 13   | Postpartum                       | Failed with IVIG       | Miscarriage | 8, curettage | No/yes |

Abbreviations: CS, cesarean section; HLH, hemophagocytic lymphohistiocytosis; IVIG, intravenous immunoglobulin; PROM, premature rupture of the membranes; SGA, small for gestational age; VD, vaginal delivery.

### TABLE 3 Obstetric and neonatal events

| Complications        | N  | %  |
|----------------------|----|----|
| Maternal outcome     |    |    |
| Maternal death       | 4  | 30.8|
| Mode of delivery     |    |    |
| Vaginal              | 6  | 46.2|
| Cesarean section     | 7  | 53.8|
| Fetal or neonatal outcome |    |    |
| Live births          | 5  | 38.5|
| Premature delivery   | 4  | 57.1|
| (< 37 weeks)         |    |    |
| PROM                 | 2  | 15.4|
| SGA                  | 1  | 7.7 |
| Fetal or neonatal death | 8 | 61.5|
| Miscarriage <20 weeks | 4 | 30.8|
| Stillbirth ≥20 weeks | 2  | 15.4|
| Neonatal mortality <1 week | 2 | 15.4|

Abbreviations: PROM, premature rupture of the membranes; SGA, small for gestational age.
| Case                  | Age (years) | Associated diagnoses                  | Treatment and outcome                      | Period of gestation (weeks) | Complications | Gestation (weeks), delivery method | Indication                     | Maternal/fetal survival |
|-----------------------|-------------|---------------------------------------|--------------------------------------------|-----------------------------|---------------|-----------------------------------|-------------------------------|-------------------------|
| Chmait et al.7        | 24          | Necrotizing lymphadenitis              | IVIG postpartum day 6                      | 29                          | SGA           | 30, CS                            | Condition worsened, breech presentation | No/yes                  |
| Teng et al.3          | 28          | AIHA                                  | Steroids failed, remission after CS        | 23                          | SGA           | 29, CS                            | Fetal distress                | Yes/no                  |
| Dunn et al.12         | 41          | Still’s disease                       | Remission with corticosteroids             | 19                          | SGA           | 30, CS                            | IUGR                           | Yes/yes                 |
| Péard et al.13        | 28          | SLE                                   | Failed with corticosteroids/IVIG, remission after delivery and third IVIG dose | 22                          | Eclampsia, cerebral hemorrhage | 30, VD                            | PPROM                          | Yes                     |
| Nakabayashi et al.14  | 30          | Unknown                               | Failed with IVIG, remission with antithrombin concentrate | 21                          | Preeclampsia, SGA | 29, CS                            | Preeclampsia, IUGR, Fetal distress | Yes/yes                 |
| Mihara et al.15       | 32          | EBV                                   | Failed with corticosteroids, remission with IVIG acyclovir, methylprednisolone | 16                          | 35, VD         |                                    |                                | Yes/yes                 |
| Hanaoka et al.16      | 33          | B-cell lymphoma                       | Failed with corticosteroids, remission with R-CHOP postpartum day 8 | 21                          | 28, CS         |                                    | Fetal distress                | Yes/yes                 |
| Chien et al.17        | 28          | Unknown                               | Failed with corticosteroids, remission after CS | 23                          | SGA           | 30, CS                            | Fetal distress                | Yes/no                  |
| Klein et al.18        | 39          | EBV                                   | Failed with steroids, CsA, etoposide, rituximab | 30                          | 31, CS         |                                    | Twins, gastrointestinal bleeding | No/yes                  |
| Goulding and Bamden19 | 27          | HSV                                   | Remission with steroids, acyclovir         | 23 + 5                      | 24, CS         |                                    | PPROM and chorioamnionitis | Yes/no                  |
| Mayama et al.20       | 28          | Parvovirus B19                        | Remission with steroids                    | 20                          | 37, VD         |                                    |                                | Yes/yes                 |
| Tumian and Wong21     | 35          | CMV                                   | Failed with steroids, IVIG, CsA, acyclovir, plasma exchange | 38                          | 38, CS         |                                    | Fetal distress, previous CS | No/yes                  |
| Samra et al.22        | 36          | Unknown                               | Remission with steroids                    | 16                          |               | Term, VD, 22, spontaneous abortion |                                | Yes/yes                 |
| Giard et al.23        | 35          | KF lymphadenitis                      | Failed with steroids and etoposide         | 20                          |               |                                    |                                | No/yes                  |
| Case                    | Age (years) | Associated diagnoses       | Treatment and outcome                                      | Period of gestation (weeks) | Complications | Gestation (weeks), delivery method | Indication                                                                 | Maternal/fetal survival |
|-------------------------|-------------|----------------------------|------------------------------------------------------------|-----------------------------|---------------|-----------------------------------|----------------------------------------------------------------------------|-------------------------|
| Fernández et al.24      | 20          | Tuberculosis               | Failed with steroids IVIG, etoposide, CsA. Remission after anti-tuberculosis treatment | 24                          | PPROM         | 29, CS                            | Breech presentation, PPROM                                               | Yes/yes                |
| Takada et al.25         | 35          | SLE                        | Remission with steroids                                     | 11                          |               | 35, VD                            |                                                                            | Yes/yes                |
| Rousselin et al.26      | 44          | Raynaud syndrome           | Remission with steroids                                     | 30                          | SGA           | 38, VD                            | IUGR oligohydramnios                                                      | Yes/yes                |
| Yildiz et al.27         | 36          | Unknown                    | Remission with steroids                                     | 29                          |               | 31 + 6, CS                        | Fetal distress                                                            | Yes/yes                |
| He et al.6              | 27          | NK/T-cell lymphoma         | Failed with steroids and etoposide. Remission after ECHOP, allo-HSCT | 30                          |               | 30 + 4, CS                        | Fetal distress                                                            | No/yes                 |
| Sarkissian et al.28     | 30          | HSV-1, CMV, EBV            | Failed with steroids and etoposide                          | 35 + 2                      | HELLP         | 35 + 2, CS                        | HELLP                                                                     | No/yes                 |
| Song et al.29           | 26          | Infection (Staphylococcus epidermidis) | Failed with corticosteroids, IVIG. Remission with etoposide | 31                          |               | 31, VD                            |                                                                            | Yes/yes                |
| Song et al.29           | 36          | Unknown                    | Remission with corticosteroids, etoposide. Remission after ECHOP, allo-HSCT | 14                          |               | Spontaneous miscarriage          |                                                                            | No/no                  |
| Song et al.29           | 30          | Angioimmunoblastic T-cell lymphoma | Failed with steroids and etoposide. Remission after ECHOP, allo-HSCT | 34                          |               | 34, VD                            |                                                                            | Yes/yes                |
| Song et al.29           | 30          | Unknown                    | Failed with corticosteroids/delivery, remission with HLH-04 regimen, DEP regimen | 30                          |               | 35, CS                            |                                                                            | Yes/yes                |
| Song et al.29           | 27          | EBV                        | Failed with steroids, remission with etoposide              | 19                          |               | NA                                |                                                                            | Yes/yes                |
| Song et al.29           | 29          | Unknown                    | Failed with corticosteroids/delivery, remission with etoposide | 30                          |               | 30, CS                            | Transverse position                                                      | Yes/yes                |
| Song et al.29           | 24          | Still’s disease            | Remission with corticosteroids, fludarabine                 | 10                          |               | 16, Induced abortion              |                                                                            | Yes/no                 |
| Song et al.29           | 24          | Unknown                    | Failed with corticosteroids and cyclosporine, remission after abortion | 17                          |               | 19, Induced abortion              |                                                                            | Yes/no                 |
| Song et al.29           | 26          | Tuberculosis               | Failed with corticosteroid, remission after anti-tuberculosis treatment | 28                          |               | 28, VD                            |                                                                            | Yes/yes                |
| Case          | Age (years) | Associated diagnoses | Treatment and outcome                          | Period of gestation (weeks) | Complications | Gestation (weeks), delivery method | Indication                | Maternal/fetal survival |
|--------------|-------------|----------------------|------------------------------------------------|-----------------------------|---------------|------------------------------------|---------------------------|------------------------|
| Song et al.29 | 20          | SLE                  | Remission with corticosteroids and cyclosporine | 10                          |               | Spontaneous miscarriage            |                          | Yes/no                 |
| Song et al.29 | 24          | Unknown              | Remission with corticosteroids                  | 36                          |               | 36, VD                            |                          | Yes/yes                |
| Song et al.29 | 29          | Unknown              | Failed with corticosteroids/delivery            | 28                          |               | 28, VD                            |                          | No/yes                 |
| Song et al.29 | 25          | EBV                  | Failed with corticosteroids/delivery            | 24                          |               | 24, Delivered                      |                          | No/no                  |
| Parrott et al.30 | 28     | SLE                  | Failed with steroids IVIG and etoposide        | 18                          | SGA           | 21 + 4, Spontaneously delivered    | IUGR                      | No/no                  |
| Parrott et al.30 | 37     | CMV                  | Remission with steroids, etoposide, acyclovir, HLH-94 | 24                          | SGA           | 37, VD                            | IUGR                      | Yes/yes                |
| Cheng et al.4  | 29          | Unknown              | Failed with steroids, remission with etoposide, corticosteroid IVIG after CS | 26 + 2                     | SGA           | 27 + 2, CS                        | Condition worsened       | Yes/yes                |
| Nasser et al.31 | 36          | HSV 2                | Remission with steroids, acyclovir              | 31                          |               | 31, CS                            |                          | Yes/no                 |
| Shukla et al.5 | 23          | Unknown              | Failed with steroids, remission after abortion  | 10                          |               | Spontaneous abortion              |                          | Yes/no                 |
| Kerley et al.32 | 33      | Unknown              | Failed with steroids, BMT, CR                   | 22                          |               | 22, VD (induced labor)            | Breech presentation     | Yes/no                 |
| Yamaguchi et al.33 | NA    | HSV 2                | Failed with steroids, remission with cyclosporine, acyclovir | Midgestation               |               | 37, CS                            |                          |                        |

Abbreviations: AIHA, autoimmune hemolytic anemia; allo-HSCT, allogenic hematopoietic stem cell transplant; BMT bone marrow transplantation; CMV, cytomegalovirus; CR, complete remission; CS, cesarean section; CsA, cyclosporine A; DEP, doxorubicin- etoposide-methylprednisolone; EBV, Epstein–Barr virus; ECHOP, etoposide/cyclophosphamidex/doxorubicin/vincristine/prednisone; HELLP, hemolysis, elevated liver enzymes, low platelet count; HLH, hemophagocytic lymphohistiocytosis; HSV, herpes simplex virus; IUGR, intrauterine growth retardation; IVIG, intravenous immunoglobulin; KF, Kikuchi-Fujimoto; NA, information not available; NK, natural killer; PPROM, premature rupture of the membranes; R-CHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; SGA, small for gestational age; SLE, systemic lupus erythematosus; VD, vaginal delivery.
with hydrocortisone (with IVIG) and CsA after induced labor and then achieved PR. The conditions of the other 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 on the 22nd day after the operation due to multiple organ failure. Case 13 was admitted to the hospital with multiple organ failure, received extracorporeal membrane oxygenation immediately after complete curettage of the uterine cavity, and died the day after delivery. 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 3. Among the 13 pregnancies, 4 women died (30.8%, 4/13), fetal or neonatal death up to 1 week after delivery occurred in 8 (61.5%) pregnancies. Six fetuses (46.2%) 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 (53.8%) pregnancies that went beyond 24 weeks of gestation (26–38 weeks), and five fetuses (38.5%) survived. The most common obstetric complication was premature delivery (57.1% of neonates), followed by SGA (7.7%, 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 4). 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.10,31

The widely used standard treatment schemes at present are HLH-1994 and HLH-2004.1,8 There is currently no guideline for HLH during pregnancy. The treatments and outcomes of patients with HLH during pregnancy in our study are summarized in Table 2. Medications should be considered during pregnancy. 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 US Food and Drug Administration (FDA). Reviewing previous reports (Table 4), almost all patients received corticosteroids, and 10 showed a curative effect. Of the 13 patients with HLH in this study, corticosteroids were used in 12, and 4 patients (with/without IVIG) showed a curative effect. 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.

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.34 Etoposide is a cell cycle-specific antitumor drug that is classified as category D by the FDA. Song et al.29 reported the use of etoposide in a pregnant patient with HLH, and no congenital malformations were found in the fetus. It is considered safe for the fetus if given during the second or third trimester. 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. 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.

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. 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
In previous studies, six patients attained remission after termination of pregnancy.\textsuperscript{3,5,13,17,29} Teng et al.\textsuperscript{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 our study, termination of pregnancy was effective in two patients. If corticosteroid/IVIG/etoposide treatment is ineffective, termination of pregnancy may be an effective method of treatment. The overall effect of termination of pregnancy is still controversial in HLH. The relationship between pregnancy and HLH requires further elucidation.

HLH during pregnancy causes significant obstetric complications to the mother and fetus. Hypofibrinogenemia is common and is one of the criteria implicated in many adverse pregnancy outcomes, such as spontaneous abortion, placental abruption, and postpartum hemorrhage.\textsuperscript{38,39} Fibrinogen plays a fundamental role in maintaining the integrity of the placenta by supporting the spread of cytotrophoblasts for the development of fetal–maternal vascularization.\textsuperscript{40,41} There is currently no consensus on the peripartum management regarding the amount of fibrinogen. More attention should be directed toward pregnant women with low fibrinogen.

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. Additionally, the details of most neonatal outcomes were relatively unclear. It is important to perform more investigations to develop a standard treatment protocol for HLH in pregnancy.

In summary, the specific mechanisms underlying HLH during pregnancy are unclear. Corticosteroids are the first choice for most patients with HLH during pregnancy. Etoposide and termination of pregnancy may then be effective for patients. 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.

Conflict of interest

The authors declare that they have no conflicts of interest.

Author Contributions

Juntao Liu and Congcong Liu designed this study. Juntao Liu provided study materials or patients. Congcong Liu, Jinsong Gao and Juntao Liu collected data. Jinsong Gao, Congcong Liu analyzed and interpreted the data. Congcong Liu wrote the manuscript. All authors discussed the results, contributed to the article and approved the final manuscript.

Data Availability Statement

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.

References

1. Henter J-I, 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. https://doi.org/10.1002.(sici)1096-911x(19970528):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 Jan 14:hcaaa011. https://doi.org/10.1093/qjmed/hcaaa011
3. Teng C-L, Hwang G-Y, Lee B-J, Wang R-C, Chou M-M. Pregnancy-induced hemophagocytic lymphohistiocytosis combined with autoimmune hemolytic anemia. J Chin Med Assoc. 2009;72:156–9. https://doi.org/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. 2020; 40:153–9. https://doi.org/10.1080/01443615.2019.1601168
5. Shukla A, Kaur A, Hira HS. Pregnancy induced haemophagocytic syndrome. J Obstet Gynaecol India. 2013;63:203–5. https://doi.org/10.1070/sjO1224-011-0073-0
6. He M, Jia J, Zhang J, Bojadlursing R, Mwamaka Sharifu I, Yu J, et al. Pregnancy-associated hemophagocytic lymphohistiocytosis secondary to NK/T cells lymphoma: a case report and literature review. Medicine. 2017;96:e9628. https://doi.org/10.1097/MD.0000000000008628
7. Chnait RH, Meimín DL, Koo CH, Huffaker J. Hemophagocytic syndrome in pregnancy. Obstet Gynecol. 2000; 95:1022–4. https://doi.org/10.1016/s0029-7844(00)00834-6
8. Henter J-I, Horne A, Aricò 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. https://doi.org/10.1002/pbc.21039
9. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic
10. Pazos M, Sperling RS, Moran TM, Kraus TA. The influence of pregnancy on systemic immunity. *Immunol. Res.* 2012;54:254–61. https://doi.org/10.1007/s12026-012-8303-9

11. Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. *N Engl J Med.* 2014;370:2211–8. https://doi.org/10.1056/NEJMra1213566

12. 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. https://doi.org/10.1179/1607845412y.0000000007

13. Pécard L, Costeado-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. https://doi.org/10.1007/s00277-007-0277-4

14. Nakabayashi M, Adachi T, Izuchi S, Sugisaki A. Association of hypecytokinemia in the development of severe preeclampsia in a case of hemophagocytic syndrome. *Semin Thromb Hemost.* 1999;25:467–71. https://doi.org/10.1055/s-2007-994552

15. Miïra 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] (article in Japanese). *Rinsho Ketsueki.* 1999;40:1258–64.

16. 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. https://doi.org/10.3816/clm.2007.n.033

17. 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. https://doi.org/10.1016/j.ijoa.2009.02.016

18. Klein S, Schmidt C, La Rosée P, et al. Fulminant gastrointestinal bleeding caused by EBV-triggered hemophagocytic lymphohistiocytosis: report of a case. *Z Gastroenterol.* 2014;52:354–9. https://doi.org/10.1055/s-0034-1366154

19. 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. https://doi.org/10.1016/j.ejogrb.2014.05.005

20. Mayama M, Yoshihara M, Kokabu T, Oguchi H. Hemophagocytic lymphohistiocytosis associated with a parvovirus B19 infection during pregnancy. *Obstet Gynecol.* 2014;124:438–41. https://doi.org/10.1097/AOG.0000000000000385

21. Tunmén NR, Wong CL. Pregnancy-related hemophagocytic lymphohistiocytosis associated with cytomegalovirus infection: a diagnostic and therapeutic challenge. *Taiwan J Obstet Gynecol.* 2015;54:432–7. https://doi.org/10.1016/j.tjog.2014.11.023

22. Samra B, Yassin M, Arnaout S, Azzi J. Idiopathic hemophagocytic lymphohistiocytosis during pregnancy treated with steroids. *Hematol Rep.* 2015;7:6100. https://doi.org/10.4081/hr.2015.6100
36. Tendron A, Gouyon J-B, Decramer S. In utero exposure to immunosuppressive drugs: experimental and clinical studies. *Pediatr Nephrol*. 2002;17:121–30. https://doi.org/10.1007/s00467-001-0776-z

37. Paziana K, Del Monaco M, Cardonick E, Moritz M, Keller M, Smith B, et al. Ciclosporin use during pregnancy. *Drug Saf*. 2013;36:279–94. https://doi.org/10.1007/s40264-013-0034-x

38. Frenkel E, Duksin C, Herman A, Sherman DJ. Congenital hypofibrinogenemia in pregnancy: report of two cases and review of the literature. *Obstet Gynecol Surv*. 2004;59:775–9. https://doi.org/10.1097/01.ogx.0000143774.04144

39. Goodwin TM. Congenital hypofibrinogenemia in pregnancy. *Obstet Gynecol Surv*. 1989;44:157–61. https://doi.org/10.1097/00006254-198903000-00001

40. Suh TT, Holmback K, Jensen NJ, Daugherty CC, Small K, Simon DI, et al. Resolution of spontaneous bleeding events but failure of pregnancy in fibrinogen-deficient mice. *Genes Dev*. 1995;9:2020–33. https://doi.org/10.1101/gad.9.16.2020

41. Iwaki T, Sandoval-Cooper MJ, Paiva M, Kobayashi T, Ploplis VA, Castellino FJ. Fibrinogen stabilizes placental-maternal attachment during embryonic development in the mouse. *Am J Pathol*. 2002;160:1021–34. https://doi.org/10.1016/S0002-9440(10)64923-1