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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

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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. 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[8]: (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 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.[9]

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	Gestational age at presentation (weeks)	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 (%)[a]
1	30	G2P1	16	Pregnancy	+	+	2.06	76	40	3.95	119/210	1500	3.06	NA	NA	+	219, 96.04%
2	24	G1P0	13	Still's disease/ CMV	+	+	2.82	79	35	1.1	930/NA	8584	NA	NA	NA	+	273, 99.86%
3	23	G1P0	12	SLE	+	+	1.31	84	69	2.79	86/164	6590	2.24	18 106	NA	+	272, 99.85%
4	22	G1P0	24	SLE/CMV	+	+	10.3	66	1	0.86	304/531	31 461	15	31 161	17%	−	292, 99.96%
5	30	G2P1	19	Unknown	+	+	0.74	53	9	1	931/2674	68 590	4.37	NA	NA	+	319, 99.99%
6	24	G2P1	28	Pregnancy	+	+	0.31	73	77	0.66	138/293	26 950	6.42	NA	NA	+	319, 99.99%
7	28	G2P2	36	Parvovirus B19	+	+	0.83	55	31	0.54	260/805	31 725	4.05	NA	NA	−	302, 99.98%
8	33	G3P2	32	Unknown	+	+	15.17	99	46	0.66	1114/712	12 799	6.35	15 511	15.95%	+	270, 99.83%
9	31	G3P0	14	SLE	+	+	0.6	76	76	1.95	582/397	22 850	1.13	2950.4	14.15%	+	258, 99.63%
10	27	G2P1	36	SLE	+	+	1.93	83	290	0.65	161/332	18 916	33.56	8202	9.32%	−	292, 99.96%
11	29	G3P2	35	Unknown	+	+	9.63	99	33	0.47	144/194	66 215	15.14	18500.8	NA	+	285, 99.93%
12	23	G2P1	23	Unknown	+	+	14.18	71	38	0.5	112/452	41 756	15.17	28 512	14.18%	+	309, 99.98%
13	31	G3P1	7	Unknown	+	−	3.38	119	57	1.29	268/351	6950	12.6	↑	NA	NA	236, 98.58%

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 × 10^9/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 × 10^9/L). and [a]Probability of HLH is estimated according to the HScore.

TABLE 2 Treatments and outcomes of patients with HLH during pregnancy

Case	Timing of diagnosis and treatment	Treatment and outcome	Complications	Gestation (weeks), delivery method	Maternal/ fetal survival
1	Prepartum	Corticosteroids	Stillbirth	20, CS	Yes/no
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	No/yes
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/no

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

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

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 (< 37 weeks)	4	57.1
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.

TABLE 4 Characteristics of patients previously reported to have HLH during pregnancy

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
Pérard 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 Barnden[19]	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 Wong[21]	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		Yes/yes
Giard et al.[23]	35	KF lymphadenitis	Failed with steroids and etoposide	20		22, spontaneous abortion		No/no

TABLE 4 Continued

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	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	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

(*Continues*)

TABLE 4 Continued

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		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)		Yes/no
Yamaguchi et al.[33]	NA	HSV 2	Failed with steroids, remission with cyclosporine, acyclovir	Midgestation		37, CS	Breech presentation	

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/cyclophosphamide/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.[10,11]

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.[3–5,13,17,29] 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 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.[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.[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.

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