Management of pregnancy-related hemophagocytic lymphohistiocytosis

Congcong Liu

Peking Union Medical College Hospital

Jinsong Gao

Peking Union Medical College Hospital

Juntao Liu (✉ liujtpumch@sina.com)

Peking Union Medical College Hospital

Research

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Abstract

Background: Pregnancy-related hemophagocytic lymphohistiocytosis (HLH) is rare, diagnosing HLH in pregnancy is difficult. There is currently no consensus on the treatment of pregnancy-related HLH. We aim to analyze and summarize the clinical characteristics of pregnancy-related HLH, and to discuss effective diagnostic and treatment options.

Methods: Thirteen patients with pregnancy-related HLH 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 (8–36 weeks). There were underlying associated diagnoses in 6 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, including 3 complicated by autoimmune diseases. Two patients completed their pregnancies, and the conditions of 2 patients were alleviated with dexamethasone and etoposide treatment. Four pregnant women died (all multiparas), and the mortality rate was 30.77% (4/13). Fetal or neonatal death up to 1 week after delivery occurred in 8 (61.54%) pregnancies, and there were 4 cases of miscarriage, 2 of stillbirth, and 2 of neonatal death. Complications also 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%). The maternal mortality rates of patients in the first, second, and third trimesters of pregnancy were 100% (1/1), 14.29% (1/7), and 40% (2/5) ($P = 0.129$), respectively, and the fetal or neonatal death rates in the trimesters were 100% (1/1), 85.71% (6/7), and 20% (1/5) ($P = 1.00$), respectively.

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

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 primary HLH, caused by genetic mutation, and secondary HLH, 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. Moreover, since diagnosis-specific treatment of HLH is closely associated with the prognosis of this disease, the potential causes of HLH in all patients need to be actively identified.

Pregnancy-related HLH is rare, 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 [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 pregnancy-related HLH. In the present study, we retrospectively analyzed the clinical data from 13 cases of pregnancy-related HLH at our hospital and emphasized the importance of rapid diagnosis and treatment.

Results

Study population

We included 13 patients with pregnancy-related HLH in this study, all of whom had singleton pregnancies, with a median gestational age of 23 weeks (range, 8–36 weeks). There was 1 case of HLH in the first trimester of pregnancy (7.70%), 7 in the second trimester (12–28 weeks; 53.85%), and 5 in the third trimester (38.46%). Four (30.77%) patients were primiparas and 9 (69.23%) were multiparas. There were other causes/related factors of HLH in 6 patients, including 1 with Still's disease complicated by cytomegalovirus (CMV) infection, 3 with systemic lupus erythematosus (SLE), 1 with SLE complicated by CMV infection, 1 with parvovirus B19 infection, 5 with unclear causes, and 2 with pregnancy-related causes. No patient recounted a family history of HLH. The patients' baseline characteristics are shown in Table 1.

Table 1
Baseline characteristics of the 13 pregnant women

Baseline characteristics	<i>N</i>	%
Age in years, median (range)	28 (22–33)	
Multipara	9	69.23
Nulliparous	4	30.77
Weeks of gestation at presentation, median (range)	23 (7–36)	
First trimester	1	7.70
Second trimester	7	53.85
Third trimester	5	38.46
Timing of diagnosis and treatment		
Prepartum	6	46.15
Postpartum	7	53.85

Clinical Symptoms And Laboratory Features

Fever and elevated ferritin levels were the most common symptom (13/13), followed by enlargement of the spleen (12/13), increased fibrin or triglyceride levels (10/13), hemophilia, a diminution in 2 or 3 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, including elevated liver enzymes (13/13), increased lactic dehydrogenase levels (13/13), and increased bilirubin levels (5/13). The copy number of CMV-DNA in 2 patients exceeded the normal range, and 1 patient was positive for parvovirus B19 (Table 2).

Table 2
Characteristics of patients with HLH during pregnancy

Case	1	2	3	4	5	6	7	8	9
Age (year)	24	23	31	30	31	24	30	27	22
Cause/associated diagnoses	Still's disease/CMV	SLE	SLE	Unknown	Unknown	Pregnancy	Pregnancy	SLE	SLE/CMV
Fever	+	+	+	+	+	+	+	+	+
Splenomegaly	+	+	+	+	-	+	+	+	+
Rash	+	-	-	+	-	+	-	-	+
WBC (10 ⁹ /L)	2.82	1.31	0.6	0.74	3.38	0.31	2.06	1.93	10.3
Hb (g/L)	79	84	76	53	119	73	76	83	66
Plt (10 ⁹ /L)	35	69	76	9	57	77	40	290	1
Fbg (g/L)	1.1	2.79	1.95	1	1.29	0.66	3.95	0.65	0.86
ALT/AST (U/L)	930/NA	86/164	582/397	931/2674	268/351	138/293	119/210	161/332	304/531
LDH (U/L)	304	515	1637	5800	5584	1071	983	1163	1037
TBIL (μmol/L)	110.6	7.2	9.5	45	96.2	13.1	19.4	126.8	11.5
Ferritin (ng/mL)	8584	6590	22850	68590	6950	26950	1500	18916	31461
Triglycerides (mmol/L)	NA	2.24	1.13	4.37	12.6	6.42	3.06	33.56	15
sCD25 (pg/mL)	NA	18106	2950.4	NA	↑	NA	NA	8202	31161
NK-cell activity	NA	NA	14.15%	NA	NA	NA	NA	9.32%	17%
Bone marrow BX	+	+	+	+	NA	+	+	-	-
Corticosteroids	+	+	+	+	-	+	+	+	+
IVIg	+	+	+	+	+	+	-	+	+
Etoposide	-	-	-	-	-	+	-	+	-
Cyclosporine	-	-	+	-	-	+	-	-	-
G/P	G1P0	G1P0	G3P0	G2P1	G3P1	G2P1	G2P1	G2P1	G1P0
Gestational age at presentation (week)	13	12	14	19	7	28	16	36	24
Timing of diagnosis and treatment	Prepartum	Prepartum	Postpartum	Prepartum	Postpartum	Prepartum	Prepartum	Postpartum	Prepartum
Complications	Miscarriage	Miscarriage	Miscarriage	Stillbirth	Miscarriage	SGA	Stillbirth		PROM, preterm labor
Gestation (week), Delivery method	19, CS	19, medical abortion	18, medical abortion	23 + 5, VD	8, curettage	31, CS	20, CS	38, CS	29, VD
Indication	Elevated liver enzymes					Breech No improvement	elevated liver enzymes	Fetal distress	
Birth weight (g)	NA	NA	NA	500 g	-	1500 g	720 g	NA	NA
Apgar scores at 1 and 5 minutes	-	-	-	-	-	4 and 7	-	10 and 10	NA
Maternal/fetal survival	YES/NO	YES/NO	YES/NO	NO/NO	NO/NO	YES/YES	YES/NO	YES/YES	YES/NO

NA information not available, CMV cytomegalovirus, SLE systemic lupus erythematosus, Hb hemoglobin (g/L), WBC white blood cell count (10⁹/L), Plt platelet aminotransferase, LDH lactate dehydrogenase, TG triglycerides (μmol/L), IVIG intravenous immunoglobulin, PROM premature rupture of the membranes, SG, cesarean section, Fbg fibrinogen

Therapy And Outcomes

As shown in Table 2, 6 of the 13 patients received treatment after being diagnosed with HLH during pregnancy. Of these, 5 patients were treated with single corticosteroids (4 patients also received intravenous immunoglobulin [IVIG]), 1 was treated with corticosteroid/etoposide, and 1 (16.7%, 1/6) died. Partial remission (PR) was achieved in 3 patients who were treated with single corticosteroids, of whom 2 (with IVIG) required termination of pregnancy because of the effects of HLH and medication during gestation. One of the latter 2 patients showed deterioration on the second day after termination of pregnancy, while the other experienced a stillbirth, underwent a cesarean section because of elevated liver enzymes, and continued to be treated after termination of pregnancy. All 3 patients ultimately achieved complete remission (CR). After dexamethasone (with IVIG) treatment, the condition of 1 patient continued to deteriorate progressively, and she spontaneously aborted and subsequently died of multiple organ failure 1 day after delivery. One patient received methylprednisolone (with IVIG) treatment without remission, and she continued corticosteroid (with IVIG) treatment after vaginal delivery, achieved a PR, and was discharged from the hospital 35 days after delivery. One patient was treated with corticosteroids/etoposide without remission, receiving a regimen of dexamethasone (with IVIG), etoposide, and cyclosporine A (CsA) after cesarean section. She achieved a PR 10 days after the operation and was then discharged from the hospital.

Seven patients were diagnosed with HLH after termination of pregnancy and began receiving treatment. One patient was treated with corticosteroids/CsA, 3 were treated with corticosteroids/etoposide, 2 were treated with single corticosteroids, and 1 was treated with extracorporeal membrane oxygenation immediately after delivery. The condition of the 5 patients still deteriorated after delivery, and 3 (42.9%, 3/7) died. Case 5 was admitted to the hospital with multiple organ failure, received extracorporeal membrane oxygenation immediately after complete curettage of the uterine cavity, and died on the first day after delivery. Case 11 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 12 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. The condition of case 8 after cesarean section deteriorated and the patient then received dexamethasone (with IVIG) and etoposide treatment, achieving a CR. Case 13 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. Case 3 began to undergo treatment with hydrocortisone (with IVIG) and CsA on the same day after induced labor, and then achieved a PR. Case 10 received corticosteroid (without IVIG) treatment after cesarean section and then achieved a PR.

Four women died (30.77%, 4/13) (all multiparas), including 1 who received treatment during pregnancy (16.7%, 1/6) and 3 who received treatment after delivery (42.9%, 3/7) ($P=0.56$, Table 3).

Table 3
Comparison of maternal and fetal outcomes in the study population

Baseline characteristics	Prepartum $N=6$	Postpartum $N=7$	P -value of difference between the 2 groups
	$N(\%)$	$N(\%)$	
Age in years, median (range)	24 (22–30)	29 (2–33)	0.105
Gestational age at presentation in week, median (range)	17.5 (12–28)	32 (7–36)	0.192
first trimester	0 (0.00)	1 (14.29)	
second trimester	5 (83.33)	2 (28.57)	
third trimester	1 (16.67)	4 (57.14)	
Gestational age in week, median (range); delivery (median)	22 (19–31)	36 (8–38)	0.347
Mode of delivery			1
Vaginal	3 (50)	3 (42.86)	
Cesarean section	3 (50)	4 (57.14)	
Outcome			
Maternal death	1 (16.67)	3 (42.86)	0.559
Fetal or neonatal death	5 (83.33)	3 (42.86)	0.266
Miscarriage < 20 weeks	2	2	
Stillbirth $\geq$ 20 weeks	2	0	
Neonatal mortality < 1 week	1	1	

Obstetric And Neonatal Events

Obstetric and neonatal events are shown in Table 4. Among the 13 pregnancies, 7 (53.85%) women delivered by cesarean section, including 2 with elevated liver enzymes, 2 with fetal distress, 1 whose condition worsened, 1 who did not respond to corticosteroids and etoposide, and 1 with a scarred uterus. Six patients underwent vaginal delivery (46.15%), 2 patients were medically aborted, and 1 patient underwent dilation and curettage at 8 weeks. Two women with stillbirths developed vaginal bleeding and spontaneous premature rupture of the membranes (PROM) with subsequent vaginal delivery, and 1 woman experienced spontaneous PROM and subsequently achieved a vaginal delivery.

With regard to fetal outcome, 6 fetuses (46.15%) were immature (8–23 + 5 weeks); there were 4 miscarriages at 8–19 weeks, and 2 stillbirths occurred at 20 and 23 + 5 weeks. There were 7 (53.85%) pregnancies that went beyond 24 weeks of gestation (26–38 weeks), and 5 fetuses (38.46%) survived. PROM occurred in cases 9 and 13 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. Fetal or neonatal death up to 1 week after delivery occurred in 8 (61.54%) pregnancies: there were 5 neonatal deaths while the mother underwent treatment during pregnancy (83%, 5/6), and 3 during treatment after delivery (42.9%, 3/7) ($P = 0.27$). The most common obstetric complication was premature delivery (57.14% of neonates), followed by SGA (7.70%, 1/13).

Maternal mortality rates of patients in the first, second, and third trimesters of pregnancy were 100% (1/1), 14.29% (1/7), and 40% (2/5) ($P = 0.129$), respectively, while fetal or neonatal death rates in the first, second, and third trimesters were 100% (1/1), 85.71% (6/7), and 20% (1/5) ($P = 1.00$), respectively.

Table 4
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 $\geq$ 20 weeks	2	15.38
Neonatal mortality < 1 week	2	15.38
<i>PROM</i> premature rupture of the membranes, <i>SGA</i> small for gestational age		

Discussion

Pregnancy-related HLH is rare, and relevant experience regarding this condition is limited owing to the small number of clinical cases; thus, the effect on the fetus from medication during pregnancy needs to be considered. Although there are presently no guidelines for diagnosing or treating pregnancy-related HLH, 5 of the 8 items need to be met according to the HLH-2004 diagnostic criteria. Diagnosing HLH is difficult upon admission, and some patients are only diagnosed after delivery.

The most common time of onset for pregnancy-related HLH was in the second trimester of pregnancy, followed by the third trimester. Approximately 3/4 of patients in the second trimester were diagnosed and received treatment during pregnancy, and 80% (4/5) of the patients in the third trimester were diagnosed and treated after the completion of pregnancy. A summary of the case reports in the literature between 1999 and 2019 showed that there were 40 cases of pregnancy-related HLH (Table 5)—including 4 (10%) in the first trimester, 21 (52.5%) in the second trimester, and 15 (37.5%) in the third trimester—with the most common onset time being the second trimester of pregnancy. A total of 75% (3/4) of patients in the first trimester of pregnancy and 85.71% (18/21) in the second trimester were diagnosed and treated before delivery, while 73.33% (11/15) patients in the third trimester of pregnancy were diagnosed and started on treatment after delivery. The maternal mortality rates in the first, second, and third trimesters were 0% (0/4), 14.29% (3/21), and 40% (6/15) ($P = 0.129$), respectively, and the fetal or neonatal death rates in the first, second, and third trimesters were 75% (3/4), 42.86% (9/21), and 6.67% (1/15) ($P = 0.006$), respectively. The collective findings from the literature and our study suggest that maternal mortality is augmented and neonatal mortality is diminished with increasing gestational age. Our hypothesis for these phenomena is that as pregnancy may be a regulatory immune state, immunologic alterations with advancing pregnancy impair the clearance of pathogens, resulting in an increased severity of disease caused by some pathogens [8, 9]. This situation may be the cause for the increase in maternal mortality in the third trimester of pregnancy. Treatment of HLH, prolongation of gestational age, and improvement in the survival rate of newborns without significant adverse effects on pregnant women and fetuses are thus important future directions for HLH treatment of patients in their first and second trimesters of pregnancy.

Table 5
Characteristics of patients previously reported with HLH during pregnancy

Case	Age (year)	Cause/associated diagnoses	Treatment and outcome	Period of gestation (week)	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	1107
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		2876
Tumian and Wong [19]	35	CMV	Failed with steroids, IVIg, CsA, acyclovir, plasma exchange	38		38, CS	Fetal distress, previous CS	
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	

NA information not available, HLH hemophagocytic lymphohistiocytosis, AIHA autoimmune hemolytic anemia, SLE systemic lupus erythematosus, CMV cytomegalovirus, 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 all transplant, CsA cyclosporine A, PPRM premature rupture of the membranes, NK natural killer, SGA small for gestational age, HELLP hemolysis, elevated liver enzymes, low platelets, CR complete remission, PR partial remission

Case	Age (year)	Cause/associated diagnoses	Treatment and outcome	Period of gestation (week)	Complications	Gestation (week), delivery method	Indication	Birth weight (g)
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. [27]	36	Unknown	Remission with corticosteroids, etoposide	14		Spontaneous miscarriage		
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	1305
Cheng et al. [4]	29	Unknown	Failed with steroids, remission with etoposide, corticosteroid IVIG after CS	26 + 2		27 + 2, CS	Condition worsened	1005

NA information not available, HLH hemophagocytic lymphohistiocytosis, AIHA autoimmune hemolytic anemia, SLE systemic lupus erythematosus, CMV cytomegalovirus, 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 all transplant, CsA cyclosporine A, PPROM premature rupture of the membranes, NK natural killer, SGA small for gestational age, HELLP hemolysis, elevated liver enzymes, low platelets, CR complete remission, PR partial remission

Case	Age (year)	Cause/associated diagnoses	Treatment and outcome	Period of gestation (week)	Complications	Gestation (week), delivery method	Indication	Birth weight (g)
Nasser et al. [29]	36	HSV 2	Remission with steroids, acyclovir	31		31, CS	Preeclampsia?	2268
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	2592
<i>NA</i> information not available, <i>HLH</i> hemophagocytic lymphohistiocytosis, <i>AIHA</i> autoimmune hemolytic anemia, <i>SLE</i> systemic lupus erythematosus, <i>CMV</i> cytomegalovirus, <i>HSV</i> herpes simplex virus, <i>IVIg</i> intravenous immunoglobulin, <i>R-CHOP</i> rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone, <i>ECHOP</i> etoposide/cyclophosphamide/doxorubicin/vincristine/prednisone, <i>VD</i> vaginal delivery, <i>CS</i> cesarean section, <i>BMT</i> bone marrow transplantation, <i>allo-HSCT</i> all-transplant, <i>CsA</i> cyclosporine A, <i>PPROM</i> premature rupture of the membranes, <i>NK</i> natural killer, <i>SGA</i> small for gestational age, <i>HELLP</i> hemolysis, elevated liver enzymes, low platelets, <i>IGT</i> intrauterine growth retardation, <i>CR</i> complete remission, <i>PR</i> partial remission								

At present, although the mechanism(s) underlying pregnancy-related HLH remains unclear, the current view is that secondary pathogenesis of HLH is due to an inability of the immune system to adequately restrict stimulatory effects of various triggers [32, 33]. The purpose of HLH treatment is to inhibit life-threatening inflammatory responses by using immunosuppressive agents and cytotoxic drugs, and the widely used standard treatment schemes at present are HLH-1994 [1] and HLH-2004 [34]. In the HLH-1994 protocol, the therapy includes dexamethasone, CsA, etoposide, and intrathecal therapy with methotrexate plus hydrocortisone. HLH-2004 was then a revision based on HLH-94, where CsA is administered at the onset instead of after 8 weeks as in HLH-94. IVIG also exhibits an anti-inflammatory effect by inhibiting complement activation, blocking the interaction of antibody Fc and macrophage Fc receptors, and neutralizing cytokines [35, 36]. Therefore, supplementation with IVIG is often used as a supportive treatment for HLH.

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. 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 or as a result of specific diseases, and 12 (31.6%, 12/38) manifested a curative effect, of whom 5 were complicated by autoimmune diseases. Of the 13 patients with pregnancy-related HLH in this study, 12 (92.3%, 12/13) were treated with corticosteroids and 5 (41.7%, 5/12) showed a curative effect, of whom 3 were complicated by autoimmune diseases. Corticosteroids thus engender a positive response in autoimmune disease-related HLH during pregnancy.

CsA may be an effective treatment for patients with pregnancy-related HLH who do not demonstrate a response to corticosteroids [31]. In our study, 2 patients were treated with CsA, including 1 with the combination of hydrocortisone and CsA, and 1 with the combination of dexamethasone, etoposide, and CsA. However, recently published results from the HLH-2004 protocol study showed that there was no significant reduction in mortality. Because CSA is associated with side effects as well as contraindications (particularly early in the disease course), the HLH-94 protocol remains the recommended standard of care [37, 38]. Etoposide is a cell cycle-specific antitumor drug that is classified as category D by the FDA, and its use in the third trimester of pregnancy does not cause neonatal malformations [39]. Song et al. [27] reported that etoposide used in patients with no response to corticosteroids/IVIg, and in 6 cases of pregnancy-related HLH, achieved remission after etoposide treatment. The initial treatment of severe patients with HLH as reported by Klein et al. showed that once the disease was defined as "high risk" and/or refractory to therapy, prompt introduction of etoposide (ideally within 4 weeks) was recommended [16]; and Parrott et al. [28] reported that etoposide was more beneficial to the patient than harmful to the fetus. In the current study, 4 patients were treated with etoposide, of whom 1 was treated during pregnancy, and we observed no abnormalities in the neonates. Our other 3 patients were treated after delivery, and 2 achieved CR, while 1 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.

Patients with pregnancy-related HLH attain remission after termination of pregnancy. Teng et al. [3] hypothesized that the pathogenesis of pregnancy-induced HLH 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 (emergency cesarean section, spontaneous abortion, or induced labor) may thus prevent the maternal condition from continuing to deteriorate and allow for timely chemotherapy. In previous studies, 6 patients (40%, 6/15 from a total of 40 cases) attained remission after termination of pregnancy [3–5, 11, 15, 27], including 4 with unclear causes, 1 complicated by SLE, and 1 complicated by autoimmune hemolytic anemia. In our study, termination of pregnancy was effective in 2 patients. However, the condition of 6 cases was exacerbated or did not improve after termination of pregnancy. The overall effect of termination of pregnancy is still controversial in HLH; if corticosteroid treatment is ineffective, termination of pregnancy may be an effective method of treatment. Thus, the relationship between pregnancy and HLH requires further elucidation.

Pregnancy-related HLH causes significant obstetric complications to the mother or fetus. In our study, 4 women underwent preterm labor, 1 had a SGA fetus, and 2 cases showed fetal distress. Previous literature depicted the incidence of SGA, preterm labor, preeclampsia/HELLP, and fetal distress at 20% (8/40), 62.5% (25/40), 7.5% (3/40), and 17.5% (7/40), respectively, which may be related to abnormal activation of macrophages. Macrophages can be specifically recruited to the maternal–fetal interface by trophoblast cells, and their versatility may be necessary in multiple pregnancy-related functions. Macrophage

activation, hyperinflammation, and pro-inflammatory cytokine secretion can also affect angiogenesis and tissue homeostasis, trophoblast invasion, and spiral artery modification. Additionally, these functional alterations can affect placental apoptosis and syncytial integrity, as well as induce preeclampsia, intrauterine growth retardation, or fetal death [40, 41].

The prognosis of secondary HLH largely depends upon underlying diseases, with a poor outcome observed for patients with malignancies [42]. Prognostic factors of early death in a cohort with adult hemophagocytic syndrome indicated that the use of etoposide as the first-line treatment tended to be associated with a better outcome [43]. Although, due to the effect of etoposide on the fetus, it is rarely used during pregnancy. However, after delivery, patients—especially those with severe conditions—may attempt etoposide use as soon as possible in order to improve their prognosis.

There are inherent biases to our study because it was a retrospective study conducted in a referral center. The condition of the majority of patients also continued to worsen at the local hospitals. Therefore, this may have generated bias in the evaluation of treatment effects. Additionally, the details governing most neonatal outcomes were relatively unclear. Therefore, we believe it to be of paramount importance to perform a prospective, multidisciplinary study on pregnancy-related HLH.

Conclusions

In summary, the specific mechanism(s) underlying pregnancy-related HLH is unclear, and early diagnosis and treatment are therefore critical for maternal survival. Corticosteroids are the first choice for most patients with pregnancy-related HLH, but for those who do not respond to corticosteroid treatment, causes and related factors need to be identified and treated accordingly. Etoposide and pregnancy termination 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. 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 Beijing, China, consecutive patients with pregnancy-related HLH who were diagnosed and treated from January 2000 to December 2019 were identified retrospectively.

All patients were diagnosed during pregnancy (at 7–36 weeks of gestation) and met the following diagnostic criteria of HLH-2004 [34]. The diagnosis of HLH was established if 1 of either criterion I or II was fulfilled, where criterion I is a molecular diagnosis consistent with HLH. Criterion II is then the fulfillment of diagnostic criteria for HLH (5/8 following criteria) as follows: (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.

Indices from clinical observations included the general condition of patients—including age, number of pregnancies and deliveries, gestational age at disease onset, gestational age and method of terminating pregnancy, and maternal and infant outcomes. Adverse events throughout pregnancy and the postnatal period were recorded, including miscarriage (spontaneous fetal loss before 20 weeks of gestation), first trimester elective abortions, and termination of pregnancy. The term “stillbirth” was used to describe fetal deaths at 20 weeks of gestation or later. Perinatal complications were preterm labor (delivery after 24 and before 37 completed weeks of gestation), SGA (birth weight < 10 th percentile), preeclampsia, eclampsia, HELLP, and PROM. Etiologies/related factors of HLH and HLH-related laboratory indices that were recorded included routine blood results, liver function, serum ferritin levels, fibrinogen levels, triglyceride levels, hemophagy, NK-cell viability, soluble CD25 levels, and the HLH treatment scheme and outcome.

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. 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. Differences between groups were assessed using the Student’s *t* 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: allogenic hematopoietic stem cell transplant

Declarations

Ethics approval and consent to participate

This study method was approved by the Peking Union Medical College Hospital Review Board. 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.

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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.

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