Hemophagocytic lymphohistiocytosis during pregnancy: a review of the literature in epidemiology, pathogenesis, diagnosis and treatment

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Abstract
Hemophagocytic lymphohistiocytosis (HLH) during pregnancy is rare; it is often misdiagnosed, resulting in a high maternal and foetal mortality rate. Herein, based on limited case reports including antepartum and postpartum cases, we reviewed the current studies of pregnancy-related hemophagocytic lymphohistiocytosis, and compared the epidemiology, aetiology, diagnosis and treatment of pregnancy-related hemophagocytic lymphohistiocytosis with non-pregnancy, enriching the understanding of hemophagocytic lymphohistiocytosis and its treatment in obstetrics.

Keywords: Diagnosis, Hemophagocytic lymphohistiocytosis, Infection, Pregnancy, Treatment

Introduction
Hemophagocytic lymphohistiocytosis (HLH) during pregnancy is rare and it is often misdiagnosed, resulting in a high mortality rate. HLH is a complex disease with rapid onset, whose severe condition, diagnosis, and treatment are characterized by tissue cell proliferation, hyper-inflammation, bone marrow hemophagocytic activity, and large amounts of inflammatory cytokines released by lymphocytes [1–5]. These characteristics are partly similar to those of pregnancy and related diseases such as preeclampsia. HLH is considered grossly underestimated and has attracted increasing attention because of its non-specific clinical manifestations, which are difficult to diagnose and life-threatening to the foetus [6]. There are many problems with the interaction between HLH and pregnancy, and its course during pregnancy, as well as its diagnostic characteristics and treatment need to be clarified.

Due to its low incidence and lack of clinical trials, most HLH cases have been reported in isolation. Only a few researchers have reported some causes of HLH during pregnancy and the effectiveness of treatment with steroids alone or with etoposide/cyclosporin A [7, 8]. However, there is no consensus on the diagnosis and treatment of HLH in pregnant women.

Therefore, we conducted this retrospective review to clarify the characteristics of HLH during pregnancy in order to propose diagnostic and management principles of HLH during pregnancy. We searched “hemophagocytic lymphohistiocytosis” OR “pregnancy” as keywords and found 4084 eligible articles from the PubMed, CNKI, EMBASE, the Cochrane library databases, and 53 studies (1.3%) that were published from 1958 to 2020. Most of the data obtained were published in English and Chinese, and the full text of the reports were screened for inclusion/exclusion into the study. Literature whose data were duplicated, non-pregnancy, could not be extracted, or were not available in their entirety was excluded. After
excluding interference and screening, we enrolled 81 patients (Fig. 1).

**Main text**

**Pathogenesis**

The pathophysiology of pregnancy-related HLH remains unclear. It may be that obstetricians do not know enough about HLH during pregnancy, and the aetiology examination of HLH patients during pregnancy is not sufficiently standardized. Among the 81 cases examined, 51 demonstrated clear etiology. Similar to non-pregnancy, infection (33/81) remained the primary factor in HLH during pregnancy, accounting for 41% of all pathogenic factors; other causes included malignancy (3/81) and genetic factors (1/81).

Infection is a major factor in pregnancy-related HLH, similar to non-pregnancy-related HLH. The Epstein–Barr virus (EBV) is the major pathogen in non-pregnancy HLH. Similarly, the EBV is the primary pathogen in pregnancy-related HLH, in pregnancy-related HLH, accounting for 30% of all infection factors. Among the 81 patients, 46 had an EBV test, and 10 were positive. Therefore, for maternal HLH, EBV should be promptly identified and treated. Although the exact mechanism whereby EBV leads to HLH is unknown, it is considered that EBV disrupts the normal function of CD8+ T cells, leading to specific cytotoxic pathways in HLH during pregnancy [9]. Other infection-associated factors, including herpes simplex virus (HSV), parvovirus, cytomegalovirus, leishmaniasis donovani, varicella zoster virus, malaria, tuberculosis...
more, the incidence rate in primipara (37/81) mothers after delivery and puerperal infection (Fig. 2c).Further-related to fluctuations in the maternal physiological state occurred within ten days after delivery, which may be the cases occurred within three days, and three-quarters remains unclear. In the postpartum stage, nearly half of with changes in immune function during pregnancy trimesters of pregnancy. Whether it is associated mainly occurs in the second (43% in all) and third (26% partum (20%) stages. In the antepartum stage, HLH pregnancy, including the antepartum (80%) and post-partum and foetal safety; delayed treatment may lead to missed opportunities for optimal treatment and irreversible multi-organ failure. However, due to the low incidence of pregnancy-related HLH, the diagnosis of HLH during pregnancy is still based on the HLH 2004 standard.

The placenta produces most cytokines; further, pregnancy itself is a systemic inflammatory response, and preeclampsia is considered a systemic inflammatory disease. Inflammatory responses and cytokine storms may induce or exacerbate HLH. Furthermore, HLH symptoms might be related to elevated β-hCG [19]. Teng et al. [21] hypothesized that the mechanism of HLH may be similar to that of preeclampsia, and that placental transport and its cytokine storm are key factors in the development of HLH during pregnancy. Additionally, similar to pregnancy-related HLH, the immature placenta releases syncytiotrophoblast components, foetal derived soluble RNA and DNA, and cytotrophoblast cells, which enter the maternal circulation, causing various immune disorders and systemic inflammatory responses [22, 23]. Therefore, it is reasonable to believe that pregnancy itself may be a factor for pregnancy-related HLH. However, there is no clinical basis and further evidence should be collected in the future.

Finally, there is a clear interaction between pregnancy and HLH. The incidence of HLH varies in terms of gestational age, number of births, and the severity of the disease. In addition, HLH can appear in any stage of pregnancy, including the antepartum (80%) and post-partum (20%) stages. In the antepartum stage, HLH mainly occurs in the second (43% in all) and third (26% in all) trimesters of pregnancy. Whether it is associated with changes in immune function during pregnancy remains unclear. In the postpartum stage, nearly half of the cases occurred within three days, and three-quarters occurred within ten days after delivery, which may be related to fluctuations in the maternal physiological state after delivery and puerperal infection (Fig. 2c). Furthermore, the incidence rate in primipara (37/81) mothers was slightly higher than that in multipara (20/81) mothers. The probable cause is maternal and foetal immunity. Contrary to non-pregnant cases, it is worth noting that 37% of all pathogenic factors were unexplained in cases of HLH during pregnancy. Pregnant women with HLH of unknown cause are difficult to treat effectively, and, more seriously, they account for a large proportion of cases. Moreover, the pregnancy itself may be a contributor, as evidenced cases that were completely relieved after pregnancy [20].

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On the other hand, HLH could have an impact on pregnancy. HLH increases the likelihood of complications during pregnancy, such as preeclampsia, postpartum haemorrhage and adverse perinatal outcomes. The possible mechanisms are as follows: (1) the influence of HLH; (2) the effect of HLH inducement on pregnancy, such as infection and rheumatic diseases; and (3) complications of HLH, such as shock and disseminated intravascular coagulation (DIC). Nevertheless because of the low incidence and insufficient epidemiological data, more insight into pregnancy-related HLH is needed.

**Diagnosis**

This study comprised 53 studies and 81 pregnancy patients with a median age of 29 years (range 20–44 years). Due to the non-specific clinical features of HLH, prompt diagnosis is often challenging. Early diagnosis of HLH during pregnancy and the timely initiation of treatment is necessary to ensure maternal and foetal safety; delayed treatment may lead to missed opportunities for optimal treatment and irreversible multi-organ failure. However, due to the low incidence of pregnancy-related HLH, the diagnosis of HLH during pregnancy is still based on the HLH 2004 standard.
Fig. 2  Pathogenesis, diagnosis and treatment of HLH during pregnancy. a In the case of HLH during pregnancy, maternal death and foetal death rate is shown by 10 × 10 dot plot. b (left) Proportion of different causes of HLH during pregnancy. (right) The proportion of specific pathogens in the factor of infection. c a Comparison of HLH in the history of pregnancy between primiparas and pluripara. b The proportion of HLH during pregnancy in different trimesters. c Proportion of hemophagocytosis in 59 patients who underwent bone marrow biopsy. d (Left) A variety of ways of delivery. (Right) The proportion of HLH occurring on different days after delivery. e Number of cases of ferritin in different grades and the corresponding proportions. d (left) Types of complications. (right) Differences in the use of medication in HLH during pregnancy.
Based on a previous analysis, a clinical diagnosis should be made, taking into consideration the ten major initial symptoms during pregnancy, which include fever, splenomegaly, hepatomegaly, jaundice, body aches, upper respiratory symptoms, fatigue, lymphadenopathy, pruritic rash, and vomiting. Serum ferritin testing is necessary, while cytokine tests can be performed conditionally. Hemophagocytic syndrome was found by bone marrow tests, and highly suspected patients need to be double-checked. In addition, a diagnostic score method has also been reported. Fardet et al. [24] verified a diagnostic score for secondary HLH. Its system includes the aetiology, organ, hyperferritinaemia, hypertriglyceridaemia, and hemophagocytosis. The web-based Delphi study also validated related diagnostic variables [25]. In this study, we found that the first symptoms of pregnancy-related HLH were non-specific and included persistent or intermittent fever (69%), which lacked specificity, followed by splenomegaly (42%), jaundice (20%), body aches (17%), upper respiratory symptoms (16%), fatigue (16%), lymphadenopathy (14%), pruritic rash (11%), and vomiting/nausea (11%). Furthermore, pregnant women usually presented to the hospital with normal blood pressure and heart rate, which worsened as the disease progressed.

Among the 81 subjects, 59 underwent biopsies (54 showed signs of hemophagocytosis and 5 were negative), and the remaining 22 were unreported. Multiple biopsy sites were reported, including the bone marrow (50 positive cases in 59 biopsy cases), spleen (2 positive cases), jejunum (1 positive case), and liver (2 positive cases). Hemophagocytosis was found in 13 patients after the second bone marrow biopsy. This lack of sensitivity indicates that hemophagocytosis does not necessarily occur in the bone marrow; rather, it may appear in any tissue other than bone marrow and does not require a positive bone marrow biopsy for diagnosis. It is important to note that a positive bone marrow biopsy may not be detected early in the course of the disease; thus, a second bone marrow biopsy could be considered.

The positive rates of hypertriglyceridemia and hypofibrinogenemia were 49% and 19%, respectively, which is half of the rate seen in non-pregnancy patients with HLH. People with ferritin levels above 500 ng/mL, 5000 ng/mL, and 10,000 ng/mL accounted for 92%, 37%, and 27%, respectively, similar to those found in non-pregnancy, as shown in Fig. 2c.

In terms of severe clinical manifestations, inadequate attention was paid to the central nervous system symptoms during pregnancy. There were eight cases of DIC and four women who demonstrated central nervous system symptoms, among whom only one underwent brain magnetic resonance imaging.

The maternal and foetal mortality rates were as high as 22% (17/77) and 40% (25/62) in the patients with available data, respectively, as shown in Fig. 2a. Foetal death accounted for the largest percentage of obstetric complications, as shown in Fig. 2d. Other complications included foetal distress, intrauterine growth retardation, oligohydramnios, pulmonary infections, gestational diabetes mellitus, foetal tachycardia, stroke, eclampsia, preterm labour, absent umbilical artery diastolic flow, and intracerebral haemorrhage.

Differential diagnosis

The diagnosis and management of HLH during pregnancy is complex. Due to the different biological factors and therapeutic methods that overlap between the haemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome; thrombotic thrombocytopenic purpura (TTP); hemolytic uremic syndrome (HUS); and HLH, it is necessary to make an accurate diagnosis [26]. Pregnancy-related HLH has clinical manifestations similar to the HELLP syndrome, such as haemolytic anaemia, elevated liver enzymes, and thrombocytopenia [27]. However, most cases of HELLP do not present with fever and hemophagocytosis changes, and its symptoms subside within a few days after delivery, whereas HLH progresses gradually [28]. Furthermore, preeclampsia is not an indicator of differentiation. Although HELLP is a complication of preeclampsia, some HELLP patients show atypical preeclampsia manifestations. Besides, HLH pregnant women can also develop preeclampsia as reported by Yamanaka et al. [29]. Thrombotic microangiopathy diseases, such as TTP, HUS, and HLH are highly correlated in clinical and laboratory tests, making them difficult to distinguish, as all patients displayed indicators, such as thrombocytopenia and anaemia. HUS is usually confined to the postpartum period, with initial signs and symptoms of renal failure. TTP usually presents with neurological impairments, such as visual impairment, epilepsy, and aphasia [30–32]. However, they demonstrated no hemophagocytosis or serum ferritin changes. Among TTP, HUS and HLH, pregnancy-related HLH has the higher mortality rate and is likely to worsen after delivery.

Treatment

Delaying treatment of HLH during pregnancy while blood and imaging results are pending can be harmful and lead to irreversible multi-organ failure. Therefore, clinicians should initiate treatment in patients suspected of hemophagocytosis and with unexplained cytopenia and fever. Current treatment options for HLH during pregnancy include general treatment, obstetric...
treatment, monoclonal antibody, and hematopoietic stem cell transplantation.

**General treatment**

The severity of these patients’ inflammatory storms requires immediate treatment of the inflammation. Treating the underlying cause, without attending to the inflammation, may result in missed treatment opportunities and disease progression. Anti-inflammatory drugs include corticosteroids and chemotherapeutic drugs, such as etoposide and cyclosporin A.

The most common and relatively safest treatment during pregnancy is high doses of corticosteroids, classified as Class C by the Food and Drug Administration (FDA), which are inactivated in the placenta and associated with a relatively low risk of birth defects. We found that 89% of the patients in our study were treated with corticosteroids, usually as an initial treatment for their anti-inflammatory effects. Multiple studies [8, 33, 34] have reported cases in which HLH during pregnancy was successfully treated with high-dose corticosteroids alone, suggesting that the benefits of these drugs far outweigh the risks. Since high-dose corticosteroids have been used safely in pregnancy, corticosteroids were the only treatment used in 47% of them, excluding the use of antibiotics. Therefore, corticosteroids are the first choice to control life-threatening hyperinflammation.

Etoposide is widely applied in non-pregnant HLH patients because it is the preferred chemotherapy in the treatment regimens of HLH-1994 and HLH-2004 [2, 3, 35]. However, due to the teratogenic nature of etoposide, there are concerns regarding its use in pregnant women [36]. Limitations of etoposide, classified as Class D by the FDA, in pregnancy-related HLH may be related to foetal toxicity and strong bone marrow suppression. Stefansdottir et al. [37] showed potential adverse effects on mouse foetal ovarian development. However, studies by several scholars [7, 38, 39] have shown that the use of etoposide would be of more benefit to the patient than harm to the foetus. Song et al. [40] suggested that achieving a balance between effective treatment and foetal safety was critical. Etoposide should be used actively but at appropriate doses and low toxicity. Women who received etoposide for HLH during pregnancy had a low recurrence rate and good long-term prognosis. In our study, etoposide was used in 32 of the 81 patients, among whom 23 women were in remission after treatment, as shown in Fig. 2d. Therefore, we recommend etoposide for severe, or steroid-ineffective cases of pregnancy-related HLH.

Cyclosporin A is also an important therapeutic agent in HLH-2004 and is classified as class C by the FDA, suggesting that it is safe for the foetus. Yamaguchi et al. [41] reported that cyclosporin A was a safe and available strategy for corticosteroid-resistant women during pregnancy. Cyclosporin A had a significant effect on the foetus without intrauterine distress or growth restriction. Intravenous injection of cyclosporin A can improve clinical outcomes [42]. In our study, cyclosporin A was used in 18 of the 81 patients, among whom 13 women were in remission after treatment, as shown in Fig. 2d. Therefore, cyclosporin A is a good choice for the treatment of HLH during pregnancy.

As pregnancy-related HLH disease has a variety of aetiologies, removing the triggers is as important as controlling the inflammatory storms. Therefore, aetiologic therapies are highly effective after the control of HLH acute inflammation, including R-CHOP for B-cell lymphoma [43], acyclovir for HSV infection [44], and HAART for human immunodeficiency virus infection [45]. Song et al. [40] reported that two patients who were screened for aetiologic cause showed long-term survival after treatment, emphasizing the importance of determining the underlying factors for treatment.

**Obstetric treatment**

Obstetric management is imperative to ensure the safety of HLH mothers and foetuses. Close monitoring of foetuses and pregnant women, including prenatal screening (such as foetal ultrasound and electronic foetal monitoring), preparing blood products before delivery, terminating pregnancy, preparing to rescue pregnant women and newborn babies after delivery, and postpartum follow-up are vital components of obstetric management. While the termination of pregnancy is an important mean of obstetric treatment, HLH itself is not an indication for termination. Teng et al. [21] reported good results after termination of pregnancy with no response to corticosteroids. The patient in the study by Shukla et al. [46] showed improvement on the second day after spontaneous abortion. However, there are many cases of successful treatment with conservative treatment and without termination of pregnancy. A significant improvement in symptoms was observed after standard treatment with HLH-1994/2004 [47], and in some cases, pregnant HLH patients were successfully treated with high-dose steroid drugs alone [8, 34, 48, 49]. A multicentre retrospective study of pregnancy-related HLH suggested that etoposide should be administered to patients who failed to respond to corticosteroids and IVIG [40]. Although there is insufficient evidence to prove that termination of pregnancy is beneficial to the remission of HLH, it should be considered if there is no response to HLH medication during pregnancy.

The decision to terminate pregnancy requires a comprehensive consideration of factors, including
the maternal condition, gestational age, disease factors, and life-threatening symptoms [36]. The severity of maternal disease plays a key role. Termination of pregnancy in a highly inflammatory state may increase the burden on the organs of pregnant women. In addition, the delivery operation itself may increase the risk to the pregnant woman; for example, delivery induced DIC may lead to postpartum haemorrhage that requires rescue. From the foetal point of view, the risk of continuing pregnancy is high, and the safety of the foetus needs to be closely monitored. Gestational age should also be considered. If foetal lungs are immature, promoting foetal lung maturation treatment is appropriate because steroids are also beneficial in the treatment of HLH. Therefore, the termination of pregnancy depends on a comprehensive consideration to ensure maternal and foetal safety.

In addition, in terms of the choice of the delivery mode, 23 of 55 women who terminated their pregnancies delivered by caesarean section, accounting for nearly half, as shown in Fig. 2c. In the 22 foetal death cases counted, there were eight therapeutic abortions, five vaginal deliveries, five spontaneous abortions, and four caesarean sections. In terms of puerperium management, breastfeeding can also affect the physical status of the mother, but it needs to be determined according to the patient’s specific situation due to the lack of data reported (Fig. 3). All our statistical data are summarized in Additional file 1.

**Fig. 3** Draw a flow chart of HLH during pregnancy

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**HLH During Pregnancy assessment and management guideline**

**Pathogenesis**
- Infection (EBV, HSV, Parvovirus, CMV)
- SLE
- Lymphoma

**Initial symptom**
- Fever
- Splenomegaly
- Hepatomegaly
- Jaundice
- Body aches
- Upper respiratory symptoms

**Complications**
- Stillbirth
- Fetal distress
- IUGR
- Oligohydramnios

**Clinical features**
- CBC, hepatic panel, fibrinogen, triglycerides, LDH, CRP, CT, ESR
- sCD25
- NK cell viability
- Ferritin
- Bone marrow biopsy
- Other tissue biopsies: liver, lymph node, masses

**Diagnosis**
- Virus check
- Rheumatic immunoassay
- Blood culture
- Genetic test
- Cardiopulmonary check
- Abdominal ultrasound
- T-spot
- Widal Test
- SAA
- Coombs Test
- PETCT
- MRI of brain

**Treatment**
- Steroids
- Globulin
- Etoposide
- CSA
- Monoclonal antibody
- Etiological treatment: antiviral antibiotics
- HLA match, HSCT

- Delivery
- Prepare blood products
- Fetal ultrasound
- Electronic fetal monitoring
- Preparation for resuscitating pregnant women and newborn babies
- Prenatal screening
- Postpartum follow-up
Conclusions

HLH during pregnancy is a rare, fatal, and often misdiagnosed disease with a high maternal and foetal mortality rate due to its non-specific clinical manifestations. Similar to non-pregnancy, EBV infection is still the first and most important contributing factor to HLH during pregnancy. The initial clinical symptoms of HLH during pregnancy are lack of specificity. Cases with negative bone marrow biopsy and high suspicion should be considered for twice biopsy. Early diagnosis, timely treatment and good obstetric management are the necessary conditions to ensure the safety of mothers and children. Finally, termination of pregnancy requires timely and comprehensive consideration. From the perspective of obstetrics, this study enriches the comprehensive understanding of HLH diagnosis and treatment. In the future, we propose to establish a global alliance for HLH during pregnancy to standardize the collection of relevant data and form a consensus guide to optimize the diagnosis and treatment of patients.

Abbreviations
allogeneic hematopoietic stem cell transplantation; AIHA: Autoimmune haemolytic anaemia; ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate aminotransferase; CMV: Cytomegalovirus; CS: Caesarean section; EBV: Epstein–Barr virus; Fib: Fibrinogen; Hb: Haemoglobin; HIV: Human immunodeficiency virus; HLH: Hemophagocytic lymphohistiocytosis; HSV: Herpes simplex virus; IUGR: Intrauterine growth retardation; LDH: Lactate dehydrogenase; M-HLH: Malignancy-associated HLH; McAb: Monoclonal antibody; NK: Natural killer; PLT: Platelets; SLE: Systemic lupus erythematosus; Soluble CD25: Soluble interleukin-2 receptor; UA: Umbilical artery; VD: Vaginal delivery; VZV: Varicella zoster virus.

Supplementary Information
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Additional file 1. Data extracted from literatures.

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Authors’ contributions
XL, QZ and HZ conceived the topic and designed the review study. LL and YC extracted the data, performed statistical analyses, and wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The data used are available from the first and corresponding authors on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors confirm there is no conflict of interest.

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References
1. Bergsten E, Horne A, Arocí M, Autogarraga I, Egele R, Filippovich AH, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. Blood. 2017;130(25):2728–38.
2. Henter JI, Samuelsson-Horne A, Arocí M, Egele R, Elinder G, Filippovich AH, et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunotherapy and bone marrow transplantation. Blood. 2002;100(7):2367–73.
3. Henter JI, Horne A, Arocí M, Egele R, Filippovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(2):124–31.
4. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamash MA, Bosch X. Adult haemophagocytic syndrome. Lancet. 2014;383(9927):1503–16.
5. Jamy G, Nunnery S, Gun S, Wiedower E, Johnson B, Yaghour M, et al. Under-recognition of hemophagocytic syndrome in United States’ rural, non-teaching hospitals. Leuk Lymphoma. 2016;57(12):2911–3.
6. Buysse S, Teixeira L, Galicer L, Mariotte E, Lemiale V, Seguin A, et al. Critical care management of patients with hemophagocytic lymphohistiocytosis. Intensive Care Med. 2010;36(10):1695–702.
7. Parrott J, Shilling A, Male HJ, Holland M, Clark-Ganheart CA. Hemophagocytic lymphohistiocytosis in pregnancy: a case series and review of the current literature. Case Rep Obstet Gynecol. 2019;2019:965367.
8. 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(6):325–8.
9. Kasahara Y, Yachie A. Cell-type specific infection of Epstein–Barr virus (EBV) in EBV-associated hemophagocytic lymphohistiocytosis and chronic active EBV infection. Crit Rev Oncol Hematol. 2002;44(3):283–94.
10. Pentheroudakis G, Pavlidis N, Castiglione M, ESMO Guidelines Working Group. Cancer, fertility and pregnancy: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2008;19(Suppl 2):i108–9.
11. Walker JW, Reinsch JF, Monforte HL. Maternal pulmonary adenocarcinoma metastatic to the fetus: first recorded case report and literature review. Pediatr Pathol Mol Med. 2002;21(1):57–69.
12. Maruko K, Maeda T, Kamitomo M, Hatae M, Sueyoshi K. Transplacental transmission of maternal B-cell lymphoma. Am J Obstet Gynecol. 2004;191(1):380–1.
13. Nishi Y, Suzuki S, Otsubo Y, Ishikawa G, Ishikawa M, Takei R, et al. B-cell-type malignant lymphoma with placental involvement. J Obstet Gynaecol Res. 2002;28(1):39–43.
14. Meugerian-Redoyan Z, Lantam L, Hopfner C, Pufldor K, Chittal S, Delso G. Anaplastic large cell lymphoma of maternal origin involving the placenta: case report and literature survey. Am J Surg Pathol. 1997;21(10):1236–41.
15. Pollack RN, Sklarin NT, Rao S, Divon MY. Metastatic placental lymphoma associated with maternal human immunodeficiency virus infection. Obstet Gynecol. 1993;81(S(Pt 2)):856–7.
22. Redman CW, Sargent IL. Pre-eclampsia, the placenta and the maternal

17. Kurtin PJ, Gaffey TA, Habermann TM. Peripheral T-cell lymphoma involving

35. Trottestam H, Horne A, Aricò M, Egeler RM, Filipovich AH, Gadner H, et al. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: report of a case and review of the literature. Orphanet J Rare Dis. 2017;12(1):42–3.

34. Mayama M, Yoshihara M, Kokabu T, Oguchi H. Hemophagocytic lymphohistiocytosis associated with cytomegalovirus infection: a diagnostic and therapeutic challenge. Taisho J Obstet Gynecol. 2015;54(4):432–7.

33. Wallace K, Harris S, Addison A, Bean C. HELLP syndrome: pathophysiology of hemolysis, elevated liver enzymes, and low platelet count. Obstet Gynecol. 2014;133(5 Pt 2):1331–42.

32. Kerley RN, Kelly RM, Cahill MR, Kenny LC. Hemophagocytic lymphohistiocytosis in pregnancy. J Obstet Gynaecol India. 2013;63(3):203–5.

31. Neave L, Scully M. Microangiopathic hemolytic anemia in pregnancy. Clin Sci. 2009;172(3):381–6.

30. Sheerin NS, Glover E. Haemolytic uremic syndrome: diagnosis and management. Br J Hosp Med. 2019;80(12):699–706.

29. Zhang J, Yang J, Wang J, Gao X, Kang P, Li S, et al. Etoposide damages female germ cells in the developing ovary. Hum Reprod. 2015;30(7):1806–15.

28. Redman CW, Sargent IL. Pre-eclampsia and the maternal systemic inflammatory response—a review. Placenta. 2003;24(Suppl A):S21–7.

27. Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. Hemodial Int. 2009;13(3):241–51.

26. Kerley RN, Kelly RM, Cahill MR, Kenny LC. Hemophagocytic lymphohistiocytosis: report of a case. J Gastroenterol Hepatol. 2015;30(4):554–60.

25. Singh Y, Wang Z, Hao Z, Lu L, Li J, Kang H, et al. Requirement for etoposide in the treatment of pregnancy related hemophagocytic lymphohistiocytosis: a multicenter retrospective study. Orphanet J Rare Dis. 2019;14(1):50.

24. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Disseminated herpes simplex virus 2-associated hemophagocytic lymphohistiocytosis in a patient in pregnancy. Obstet Gynecol. 2005;105(5 Pt 2):1241–4.

23. Wahbi A, Gravelle J, Néel A, Joubert M, Masseau A, Joly GM, et al. Macrophage inflammatory cytokine in the development of severe preeclampsia in a case of hemophagocytic lymphohistiocytosis. Rev Med Interne. 2015;36(8):555–7.

22. Redman CW, Sargent IL. Pre-eclampsia, the placenta and the maternal systemic inflammatory response—a review. Placenta. 2003;24(Suppl A):S21–7.

21. Thurnam NR, Wong CL, Pinnix CC, Andraos TY, Milgrom S, Fanale MA. The management of macrovesicular hepatic steatosis caused by EBV-2 infection: a diagnostic dilemma. Cureus. 2018;10(3):e2352.

20. Hannebicque-Montaigne K, Le Roc'h A, Launay D, Coulon C, Deruelle P, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014;66(9):2613–20.

19. Neave L, Scully M. Microangiopathic hemolytic anemia in pregnancy. Obstet Gynecol. 2014;124(2 Pt 2 Suppl 1):438–41.

18. Kurtin PJ, Gaffey TA, Habermann TM. Peripheral T-cell lymphoma involving the placenta. Cancer. 1992;70(12):2963–8.

17. Kurtin PJ, Gaffey TA, Habermann TM. Peripheral T-cell lymphoma involving the placenta. Cancer. 1992;70(12):2963–8.

16. Tsujimura T, Matsumoto K, Aozasa K. Placental involvement by maternal non-Hodgkin's lymphoma. Arch Pathol Lab Med. 1993;117(3):325–7.

15. Kurtin PJ, Gaffey TA, Habermann TM. Peripheral T-cell lymphoma involving the placenta. Cancer. 1992;70(12):2963–8.

14. Catlin EA, Roberts JD Jr, Erana R, Preffer FI, Ferry JA, Kellher AS, et al. Transplacental transmission of natural-killer-cell lymphoma. N Engl J Med. 1999;341(2):85–91.

13. Wang LY, Hu J, Ramsingh G, Theodory B, Yaghmour B, Vergara-Lluri M, et al. A case of recurrent pregnancy-induced adult onset familial hemophagocytic lymphohistiocytosis: World J Oncol. 2018;9(4):123–7.

12. Tsunimura NR, Wong CL. Pregnancy-related hemophagocytic lymphohistiocytosis associated with cytomegalovirus infection: a diagnostic and therapeutic challenge. Taisho J Obstet Gynecol. 2015;54(4):432–7.

11. Redman CW, Sargent IL. Pre-eclampsia, the placenta and the maternal systemic inflammatory response—a review. Placenta. 2003;24(Suppl A):S21–7.

10. Rousselin A, Alavi Z, Le Moigne E, Renard S, Tremouilhac C, Delluc A, et al. Hemophagocytic syndrome in pregnancy: case report, diagnosis, treatment, and prognosis. Clin Case Rep. 2017;5(11):1756–64.

9. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Disseminated herpes simplex virus 2-associated hemophagocytic lymphohistiocytosis: report of a case. J Gastroenterol Hepatol. 2015;30(4):554–60.

8. Samra B, Yasmin M, Arnaout S, Azzi J. Idiopathic hemophagocytic lymphohistiocytosis during pregnancy treated with steroids. Hematol Rep. 2015;7(3):6100.

7. Takada H, Kimura N, Yoshishahi-Nakazato Y, Kawaihata K, Kosaka H. Dicoid lupus erythematosus complicated with pregnancy-induced hemophagocytic syndrome. Intern Med. 2017;56(12):1581–3.

6. 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(2):153–9.

5. 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(4):413–6.

4. Giard JM, Decker KA, Lai JC, Gill RM, Logan AC, Fix OK. Acute liver failure secondary to hemophagocytic lymphohistiocytosis during pregnancy. ACG Case Rep J. 2016;3(4):e162.

3. Gill DS, Spencer A, Cobcroft RG. High-dose gamma-globulin therapy in the reactive haemophagocytic syndrome. Br J Haematol. 1994;88(1):204–6.

2. Hannebique-Montaigne K, Le Roch A, Launay D, Coulon C, Deruelle P, Langlois S. Haemophagocytic syndrome in pregnancy: a case report. Ann Fr Anesth Reanim. 2011;30(3):239–42.

1. He M, Jia J, Zhang J, Beejadhursing R, Mwamaka Sharifu L, Yu J, et al. Pregnancy-associated hemophagocytic lymphohistiocytosis during pregnancy treated with steroids. Hematol Rep. 2020;12(3):6100.

1. He M, Jia J, Zhang J, Beejadhursing R, Mwamaka Sharifu L, Yu J, et al. Pregnancy-associated hemophagocytic lymphohistiocytosis secondary to hemophagocytic syndrome during pregnancy treated with steroids. Hematol Rep. 2020;12(3):6100.

1. Kim JY, Yun JY, Kim HY, Park HY, Kim H, Lee S, et al. Identification of Epstein–Barr virus-2 infection: a diagnostic dilemma. Cureus. 2018;10(3):e2352.

1. Kim JY, Yun JY, Kim HY, Park HY, Kim H, Lee S, et al. Identification of Epstein–Barr virus-2 infection: a diagnostic dilemma. Cureus. 2018;10(3):e2352.
62. Pawar S, Ragesh R, Nischal N, Sharma S, Panda PK, Sharma SK. Unique Triad of “Pregnancy, Kala Azar and Hemophagocytic Lymphohistiocytic Syndrome from a Non-Endemic Region.” J Assoc Phys India. 2015;63(6):65–8.
63. Tsuda H, Shirono K, Shimizu K, Shimomura T. Postpartum parovirus B19-associated acute pure red cell aplasia and hemophagocytic syndrome. Rinsho Ketsueki. 1995;36(7):672–6.
64. Yildiz H, Vandercam B, Thissen X, Komuta M, Lanthier N, Debieve F, et al. Hepatitis during pregnancy: a case of hemophagocytic lymphohistiocytosis. Clin Res Hepatol Gastroenterol. 2018;42(3):e49–55.
65. Yoshida S, Takeuchi T, Itami Y, Hata K, Watanabe K, Shoda T, et al. Hemophagocytic syndrome as primary manifestation in a patient with systemic lupus erythematosus after parturition. Nihon Rinsho Meneki Gakkai Kaishi. 2009;32(1):66–70.

66. Gonzalez EG, Olvera HR, Gonzalez VMV, Damian RF. Hemophagocytic syndrome secondary to an infection with parovirus B19. Rev Chil Obstet Ginecol. 2008;73:406–10.
67. Ishida A, Matsumoto J, Kobayashi S, Kikuchi S, Harada Y, Hosone M, et al. A case of reactive hemophagocytic syndrome which occurred during treatment of hyperemesis. Kanto J Obstet Gynaecol. 1996;33:51–4.

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