Haemophagocytic lymphohistiocytosis in pregnancy

Harold Wilson-Morkeh[1], Charlotte Frise[2,3] and Taryn Youngstein[1,4] (iD)

Abstract

Haemophagocytic lymphohistiocytosis is a life-threatening systemic inflammatory syndrome defined by persistent fever, cytopenia and multi-organ dysfunction. Primary haemophagocytic lymphohistiocytosis classically presents in childhood as a result of genetically abnormal perforin or inflammasome function, leading to the aberrant release of pro-inflammatory cytokines causing a hyperinflammatory state. Secondary haemophagocytic lymphohistiocytosis is an acquired phenomenon occurring at any age as a result of immune dysregulation to a specific trigger such as infection, haematological malignancy or autoimmune disease. Secondary haemophagocytic lymphohistiocytosis occurring in the pregnant woman represents a diagnostic challenge and carries a significant mortality. This has led to its first inclusion in the fourth Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the United Kingdom annual maternal report in 2017. This article presents an overview of haemophagocytic lymphohistiocytosis, reviews the literature on haemophagocytic lymphohistiocytosis in pregnancy, suggests diagnostic pathways and explores the safety and efficacy of existing and potential treatment strategies for haemophagocytic lymphohistiocytosis occurring during pregnancy.

Keywords

Maternal death, haemophagocytosis, inflammation

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a life-threatening systemic inflammatory syndrome defined by persistent fever, cytopaenia and multi-organ dysfunction. The terms 'haemophagocytic syndrome' and 'macrophage activation syndrome' may also be used – the latter particularly in the context of autoimmune disease.[1]

HLH is classically divided into two categories; familial or primary HLH (pHLH), which most commonly presents in childhood and is caused by abnormal function of perforin and the inflammasome, leading to the aberrant release of pro-inflammatory cytokines.[2] The second and more common form of HLH is known as secondary HLH (sHLH). This is an acquired phenomenon occurring at any age as a result of immune dysregulation to a specific trigger in the context of reduced, rather than absent, cytolytic protein function.[3] Although pHLH may present in adolescents and young adults, sHLH is by far the most prevalent subtype in women of child-bearing age. However, the distinction between genetic mutations resulting in pHLH and the possible aetiologies of sHLH is likely to be an oversimplification; heterozygous perforin pathway mutations have been described in those with sHLH, particularly in Epstein-Barr virus- (EBV) driven adult-onset sHLH, as well as other mutations in pathways leading to hyperinflammation such as *NLRC4* mutations impairing inflammasome activity and *SH2P1A* mutations leading to impaired viral response.[2]

Typically, there is a delay in the diagnosis of HLH; in part due to the similarity in presentation to sepsis and other causes of multiorgan failure.[4] Common triggers of sHLH include infection, autoimmune conditions and malignancy (Table 1).[5] Secondary HLH is challenging to diagnose and it is also challenging to treat. Multidisciplinary discussion is best sought early given the associated high mortality. The Histiocytosis UK Haemophagocytosis Across Specialty Collaboration (HASC) is a national initiative to create local and regional multidisciplinary teams to aid in the management of these women to improve outcomes.[6–8] However, alerting the local and regional specialist teams relies on the treating clinicians being vigilant to the possibility of the diagnosis and this is a challenge due to its rarity.

In the UK between 2013 and 2015, 556 women died during pregnancy or up to one year postpartum. Of these, four (0.72%) died as a consequence of HLH.[9] Thus, HLH occurring in pregnancy is thankfully rare but is associated with a poor prognosis. It is generally accepted that early treatment of evolving HLH is associated with

[1]Department of Rheumatology, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, UK
[2]Fetal-Maternal Medicine Unit, Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital, Oxford, UK
[3]De Swiet's Obstetric Medicine Centre, Imperial College Healthcare NHS Trust, Queen Charlotte's and Chelsea Hospital, London, UK
[4]National Heart and Lung Institute, Imperial College London, London, UK

Corresponding author:
Taryn Youngstein, National Heart and Lung Institute, Imperial College London, London, UK.
Email: Taryn.youngstein@nhs.net

Table 1. Causes of HLH.[2,4,5]

Causes of HLH
Primary mutations
Defects in cytolytic function:
PRF1 (10q21-22), *UNC13D* (17q2), *STX11* (6q24), *STXBP2* (19p13), *RAB27A* (15q21), *LYST* (1q42-43), *SH2D1A* (Xq24-25)
Defects in inflammasome regulation:
BIRC4 (Xq25), *NLRC4* (2p22.3)
Secondary aetiologies
Infections:
Viruses – EBV, CMV, HSV, HHV-6 and -8, VZV, hepatitis, HIV, parvovirus B19, influenza A and B, adenovirus, enterovirus, dengue, Ebola and *others*
Bacteria – *Mycobacteria* spp., *Rickettsia* spp., *Staphylococcus* spp., *Escherichia coli*, *Legionella* spp. and *others*
Parasites – *Leishmania* spp., *Plasmodium* spp., *Toxoplasma* spp. and *others*
Fungi – *Aspergillus* spp., *Candida* spp., *Histoplasma* spp, *Pneumocystis jiroveci* and *others*
Autoimmune conditions:
SLE, sJIA, AOSD, RA, systemic vasculitides, periodic fever syndromes, IBD and *others*
Malignancy:
Haematological – T-cell, NK-cell, B-cell or Hodgkin's lymphoma, leukaemia and *others*
Solid organ tumours
Miscellaneous:
Transplantation – Solid organ or HSCT
Iatrogenic – Immunosuppression, vaccination, surgery, haemodialysis
Pregnancy

AOSD: adult-onset Still's disease; CMV: cytomegalovirus; EBV: Epstein-Barr virus; HHV: human herpesvirus; HIV: human immunodeficiency virus; HSCT: haematopoietic stem cell transplantation; HSV: herpes simplex virus; IBD: inflammatory bowel disease; NK: natural killer; RA: rheumatoid arthritis: sJIA: systemic juvenile inflammatory arthritis; SLE: systemic lupus erythematosus; spp.: species; VZV: varicella zoster virus.

better outcomes and as such raising awareness of this condition is a crucial start to improve outcomes.[5]

Pathophysiology

In immunocompetent individuals, natural killer (NK) cells and cytotoxic T-lymphocytes (CTLs) eliminate infected cells by a perforin-dependent pathway.[10] Cytotoxic cells contain secretory lysosomes that themselves contain perforin and granzymes. When these cells are activated their lysosomes are transported along microtubules toward the synapse between effector and target cell before they can release their contents into the synapse. The perforin and granzymes subsequently mediate apoptotic target cell death resulting in a down-regulation of the immune response.[10] This process is interrupted in pHLH due to genetic mutations leading to abnormal perforin function and thus an inability to destroy the diseased antigen-presenting cell (APC). Genetic variants, such as low NK cell numbers, may also contribute to individual susceptibility in those who develop sHLH[11]. Furthermore, some pathogens that persist in histiocytes such as *Mycobacterium tuberculosis* or *Leishmania* can directly activate toll-like receptors while others, like certain viruses, have developed complex immune evasion strategies that can interfere with NK and CTL cytotoxicity.[10] Failure to clear such potential antigen triggers from infected, tumour or autoimmune cells leads to uncontrolled activation and proliferation of T-lymphocytes, macrophages and pro-inflammatory cytokines, particularly interferon-gamma (IFN-γ), tumour necrosis factor-alpha (TNF-α), interleukin-10 (IL-10),
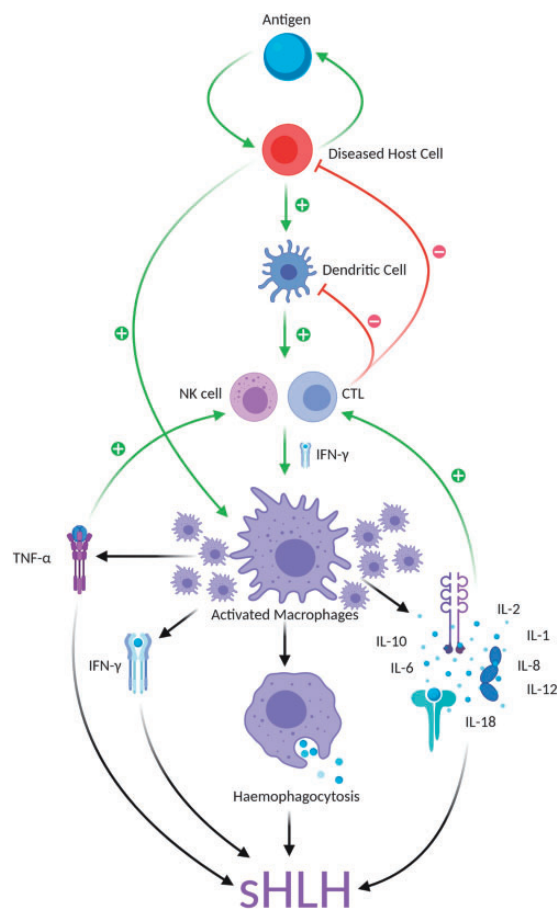

Figure 1. Pathophysiology of sHLH. CTL: cytotoxic T-lymphocyte; IFN-γ: interferon gamma; IL: interleukin; NK: natural killer; sHLH: secondary haemophagocytic lymphohistiocytosis; TNF-α: tumour necrosis factor alpha.

IL-12, IL-18. This leads to a combination of hyperinflammation, end-organ damage and haemophagocytosis resulting in the clinical manifestations of HLH. The pathophysiology of sHLH will depend on the aetiology but shares the final common pathway of hyperinflammation and organ dysfunction (Figure 1).

HLH in pregnancy

Primary HLH typically presents in childhood and the diagnosis is often established prior to any pregnancies; however, there is increasing awareness that late onset disease can occur, and genetic testing is, therefore, considered in all cases of HLH in pregnancy. During pregnancy, maternal immune regulation is under additional stress. The role of the placenta is key to acting as an immunological barrier between mother and the semi-allogeneic fetus.[12] There is evidence that a degree of inflammatory stimulus exists in all pregnancies stemming from the apoptotic debris shed from the syncytial surface of the placenta.[13] In specific contexts, the mechanisms that keep this stimulus in check can fail leading to immune dysregulation and hyperinflammation as is observed in pregnancy pathologies such as pre-eclampsia. This context provides a favourable environment for potential secondary HLH triggers such as infection or pre-existing autoimmune diseases such as systemic lupus erythematosus.[14]

Clinical presentation

sHLH is characterised by persistent fever, organ dysfunction, lymphadenopathy and hepato- and/or splenomegaly. Fever is almost universally described, but otherwise the presenting clinical signs and symptoms in adult women with HLH are less typical than in children.[5,15] Importantly, sHLH can arise in a subacute manner, with a gradual amalgamation of features rather than the florid acute presentation more frequently recognised at the point of multiorgan failure.[5]

To date, 36 cases of sHLH in pregnancy have been reported (Table 2). Clinical descriptors are available for 31 cases showing mostly non-specific presentations that could have been due to sepsis alone and other symptoms and signs that could be due to physiological changes in pregnancy or pregnancy-specific complications. In 26 cases (72% of the tabulated reports), enlargement of the liver, spleen or both is described. Splenomegaly is rarely observed in sepsis alone and should alert the clinician to an alternative underlying disease process such as lymphoma or EBV infection, but this is problematic in pregnancy as mild splenomegaly is a normal finding;[4] 48% reported either jaundice or liver function test derangement, the latter common in pregnancy. Furthermore, sHLH has been known to lead to other sequelae of liver pathology, namely encephalopathy and ascites.[50] It is also important to note the prevalence of central nervous system (CNS) involvement. Although poorly documented in this cohort, neurological symptoms are an established phenomenon within HLH with a wide spectrum of severity witnessed at presentation.[5] This can range from mild cognitive impairment and delirium to more severe CNS manifestations such as seizures, meningoencephalitis, ataxia, hemiplegia and cranial nerve palsies.[51] CNS involvement is an independent prognostic marker in paediatric HLH.[52]

Pulmonary manifestations of sHLH are common but may contribute to the diagnostic delay given the risk of attributing these symptoms to other, more common, diagnoses. A national retrospective cohort study identified lung involvement in 54% of cases with dyspnoea and cough occurring most frequently.[53] These symptoms were not frequently represented in published cases of sHLH in pregnancy (Table 2). However, the authors recommend high clinical suspicion for those with these symptoms and supportive radiological changes such as interstitial infiltrates with centrilobular nodules, ill-defined consolidation and localised ground-glass opacities on chest imaging.[53]

A wide spectrum of rashes has been reported in HLH ranging from non-specific erythematous macules to petechiae or purpura. In large non-pregnant cohorts, 25% of adults with HLH have cutaneous involvement.[5] Only one case of pregnancy-associated sHLH reported a diffuse erythematous macular rash at presentation.[31] Nodular lesions should raise suspicion of associated T-cell lymphoma.[5]

Diagnosis

The diagnosis of HLH can be difficult and a number of diagnostic criteria exist. The most widely used diagnostic criteria, HLH-2004, were established for paediatric women under 18 years of age (Table 3).[54] To date, there are no validated criteria for diagnosis of HLH in adults, although there is a composite probability score for sHLH, the HScore, which is commonly used but has not been validated in pregnancy.[2] The HScore uses clinical parameters, common laboratory values and bone marrow findings dependent on their HLH specificity and calculates a probability score (Table 4).[55] The higher the HScore out of a total of 337, the higher the likelihood of HLH. It should be further highlighted, however, that there is currently no well-validated means of diagnosing HLH in adult women, and that all available paradigms (including HScore) are limited by their lack of specificity for HLH. Many critically ill women will score highly using these paradigms whether they have HLH or not.[56]

Importantly, not all markers used in these scoring systems are routinely checked and they may be initially normal. Trends of biochemical values over time can also be revealing. We suggest the measurement of serum ferritin in any individual who is unwell and has a fever. Subsequently, the other markers of HLH, such as serum lipids and more specific tests such as the soluble interleukin-2 receptor can be requested (Figure 2). Ferritin is a glycoprotein that stores iron which it releases in a controlled manner in the absence of inflammation.[57] It is also an acute phase reactant, and as such is non-specifically elevated in a wide range of inflammatory states, including acute infection, malignancy, chronic kidney disease and a variety of autoimmune conditions.[58] During pregnancy, the serum ferritin initially rises in women with adequate iron stores at conception reaching a peak of approximately 230 μg/L during the second trimester.[57,59] This is followed by a progressive fall by 32 weeks due to haemodilution and mobilisation of iron to approximately half of the pre-pregnancy levels, before a further mild elevation in the third trimester.[57,60] Marked hyperferritinaemia (>10,000 μg/L) is 96% specific and 90% sensitive for HLH in the paediatric population.[61] It is less specific for HLH in adults, but significantly elevated levels should still raise suspicion.[62] However, in some adults, even with severe life-threatening HLH, milder elevations are observed.[2] Values between 7000 and 10,000 μg/L are often reported in this context, while a separate analysis of 50 adult women with HLH revealed a median ferritin level on presentation of 5823 μg/L.[62]

Soluble CD25 (sCD25), the soluble interleukin-2 receptor (sIL-2R) is a useful diagnostic marker for HLH especially in paediatric populations but is not yet readily available in all laboratories and its use in pregnancy has not been validated. sCD25 is a heterotrimeric transmembrane protein that is upregulated on activated T-cells, thus high levels are found in HLH, lymphoma and other conditions where T-cell activation is prevalent.[63] The test itself is based on a low-cost commercially available assay. A recent study has shown that the specificity of sCD25 in adults fails to match that seen in the paediatric population.[64] Thus, further work is required in adult cohorts with and without HLH to determine more accurate sensitivity and specificity values for this assay. It is also notable that the extent of elevation of sCD25 above 10,000 U/ml has not been shown to be of prognostic significance.[63]

Pregnancy will alter the interpretation of some of the biochemical markers typically used in the diagnosis of HLH. In the HScore, it is the ferritin and triglycerides that confer the most diagnostic weight. A pregnant woman with persistent fever and cytopaenia affecting at least 2 peripheral blood lineages presents a particular diagnostic challenge because, as well as infection, a number of pregnancy-specific conditions may present similarly. These include acute fatty liver of pregnancy and haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome. Indeed, sHLH and HELLP syndrome may coexist, thus a high degree of suspicion is warranted.[45] Lipids including cholesterol and triglycerides tend to increase in pregnancy and are infrequently measured. The normal ranges have not been established and so while it is appropriate to measure triglycerides if HLH is suspected in pregnancy, the results should be interpreted with caution.

In all cohorts of sHLH, including those occurring in pregnancy, many cases are initially treated for sepsis. Indeed, there is a known subset of septic women whose infection will cause an aberrant cytokine cascade due to immune dysregulation, resulting in the clinical syndrome of sHLH. Furthermore, sHLH can further predispose to sepsis, creating a diagnostic and therapeutic challenge. The presentation of the two syndromes may be identical, with multi-organ failure and disseminated intravascular coagulopathy (DIC) occurring in severe phenotypes, making it necessary to consider sHLH in any

Table 2. Reported cases of sHLH in pregnancy.

Reported cases of pregnancy-associated sHLH

Case number	Authors	Age (years)	Obstetric history	Gestational age (weeks)	Aetiology	Clinical presentation and laboratory findings	Treatment (except antibiotics)	Maternal outcome	Mode of delivery and fetal outcome
1	Gill et al.[16]	30	–	18	–	Fever, hepatomegaly, pancytopenia	IVIg	Remission	40/40 VD – survived
2	Tsuda et al.[17]	–	–	–	Parvovirus B19	–	–	–	–
3	Yamanaka et al.[18]	–	–	36	–	–	Steroids, IVIg, AT III	Remission	Survived
4	Ishida et al.[19]	31	–	–	Hyperemesis	–	Steroids, IVIg	Death	22/40 – IU death
5	Mihara et al.[20]	32	–	16	EBV	Fever, pancytopenia, elevated ferritin, LDH, sIL-2R	Steroids, aciclovir IVIg, gabexate mesilate	Failure Remission	35/40 VD – survived
6	Nakabayashi et al.[21]	30	–	21	Pre-eclampsia	Fever, pancytopenia, elevated ferritin, LDH, LFTs	IVIg AT III	Failure Remission	29/40 CS – survived
7	Chmait et al.[22]	24	G2 P1	29	EBV	Fever, pancytopenia, elevated LFTs	IVIg, aciclovir, CS	Death	30/40 CS – survived
8	Yamaguchi et al.[23]	–	–	–	HSV-2	Fever, pancytopenia, elevated ferritin, TG, sIL-2R	Steroids CsA	Failure Remission	40/40 VD – survived
9	Hanaoka et al.[24]	33	G1 P0	21	B-cell lymphoma	Fever, hepatosplenomegaly, pancytopenia, elevated ferritin, TG, LDH, sIL-2R	R-CHOP, HSCT	Remission	28/40 CS – survived
10	Perard et al.[25]	28	G4	22	SLE	Fever, pancytopenia, elevated ferritin, TG	Steroids IVIg	Failure Remission	30/40 VD – survived
11	Gonzalez et al.[26]	27	–	22	Parvovirus B19	–	Steroids, AT III	Remission	36/40 – survived
12	Chien et al.[27]	28	G1 P0	23	–	Fever, bicytopenia, elevated TG	CS delivery	Remission	28/40 CS – survived
13	Teng et al.[28]	28	G1 P0	23	AIHA	Fever, bicytopenia, elevated ferritin, TG, LDH, sIL-2R	Steroids	Failure	29/40 CS – death
14	Yoshida et al.[29]	33	–	PP	SLE	–	TOP	Remission	Survived
15	Arewa and Ajadi[30]	31	G1 P0	21	HIV and malaria	Fever, bicytopenia, jaundice	Antimalarials, HAART, VD	Remission	40/40 VD – survived
16	Dunn et al.[31]	41	–	19	AOSD	Fever, rash, headache, anaemia, elevated ferritin, TG, LDH, LFTs	Steroids, CS	Remission	30/40 CS – survived (twins)
17	Hannebicque-Montaigne et al.[32]	21	–	29	SLE	Fever, pancytopenia, elevated ferritin, TG	Steroids, IVIg	Remission	38/40 VD – survived
18	Kim et al.[33]	29	–	12	SLE	Fever, pancytopenia, elevated ferritin, TG, LDH	CsA, Splenectomy	Remission	14/40 TOP – death
19	Komaru et al.[34]	36	G1 P0	40+38d	Sjogren's	Splenomegaly, bicytopenia, jaundice, elevated ferritin, bilirubin, LDH, sIL-2R	Steroids	Remission	40/40 VD – survived
20	Shukla et al.[35]	23	G1 P0	10	–	Fever, hepatosplenomegaly, pancytopenia, elevated ferritin, TG, bilirubin	Steroids EPL	Failure Remission	10/40 EPL – death
21	Goulding et al.[36]	27	G1 P0	23	HSV-2	Fever, pancytopenia, elevated ferritin	Steroids, aciclovir, Valaciclovir	Remission	24/40 CS – death

(continued)

Table 2. Continued.

Reported cases of pregnancy-associated sHLH

Case number	Authors	Age (years)	Obstetric history	Gestational age (weeks)	Aetiology	Clinical presentation and laboratory findings	Treatment (except antibiotics)	Maternal outcome	Mode of delivery and fetal outcome
22	Klein et al.[37]	39	–	30	EBV	Pancytopaenia, elevated ferritin, sIL-2R	Steroids, CsA, etoposide, RTX	Death	31/40 CS – death (twins)
23	Mayama et al.[38]	28	G2 P2	19	Parvovirus B19	Fever, pancytopenia, elevated ferritin, LDH	Steroids	Remission	37/40 VD – survived
24	Samra et al.[39]	36	–	16	–	Fever, pancytopenia, elevated ferritin, TG	Steroids	Remission	40/40 VD – survived
25	Tumian and Wong.[40]	35	G2 P1	38	CMV	Fever, anaemia, jaundice, elevated ferritin, TG, LDH, LFTs, sIL-2R	CS delivery, steroids, CsA	Death	38/40 CS
26	Giard et al.[41]	35	G2 P1	13	–	Fever, pancytopenia, jaundice, elevated ferritin, TG, LFTs, sCD25	Steroids, etoposide	Death	22/40 TOP – death
27	Ota et al.[42]	26	G1 P0	23	Liver abscess	Fever, thrombocytopaenia, elevated ferritin, TG, LDH, LFTs, sIL-2R	Nil	Death	23/40 – IU death
28	He et al.[43]	27	G2 P0	30	NK/T-cell lymphoma	Fever, splenomegaly, pancytopenia, elevated ferritin, LDH, LFTs	Steroids, etoposide, RTX, CS delivery, splenectomy	Death	30/40 CS – survived
29	Ikeda et al.[44]	32	–	11	EBV	Fever, bicytopenia, elevated ferritin	Steroids, etoposide, CsA	Remission	11/40 EPL – death
30	Kerley et al.[45]	33	G1 P0	22	–	Fever, bicytopenia, elevated ferritin, LDH, LFTs	Steroids Delivery, etoposide, BMT	Failure Remission	22/40 VD – death
31	Rousselin et al.[46]	44	G1 P0	30	–	Fever, hepatomegaly, pancytopenia, elevated ferritin, TG, LDH, LFTs	Steroids	Remission	38/40 VD – survived
32	Nasser et al.[47]	36	G7 P2	31	HSV-2	Fever, splenomegaly, thrombocytopaenia, elevated ferritin, LDH, LFTs	Steroids, aciclovir, Delivery	Remission	CS – death
33	Cheng et al.[48]	–	–	26	–	Fever, bicytopenia, elevated ferritin, TG	Steroids, etoposide	Remission	27/40 TOP – death
34	Parrott et al.[14]	28	G2 P1	18	SLE	Fever, splenomegaly, pancytopenia, elevated ferritin, LFTs, sIL-2R, stroke	Steroids, etoposide, IVIg, CsA	Failure	21/40 VD – IU death
35	Parrott et al.[14]	37	G4 P3	24	CMV	Fever, thrombocytopaenia, jaundice, elevated ferritin, TG, LFTs, bilirubin, LDH, sIL-2R	Steroids, etoposide	Remission	37/40 VD – survived
36	Yip et al.[49]	23	G2 P1	22	–	Fever, pancytopenia, elevated ferritin, TG	Steroids, IVIg Anakinra	Failure Remission	31/40 CS – survived

AOSD: adult-onset Still's disease; AT III: antithrombin III; BMT: bone marrow transplantation; CMV: cytomegalovirus; CS: caesarean section; CsA: ciclosporin A; d: days; EBV: Epstein-Barr virus; EPL: early pregnancy loss; G: gravida; HAART: highly active anti-retroviral therapy; HIV: human immunodeficiency virus; HSCT: haematopoietic stem cell transplantation; HSV: herpes simplex virus; Ig: immunoglobulin; IU: intrauterine; IVIg: intravenous immunoglobulin; LFTs: liver function tests; LDH: lactate dehydrogenase; NK: natural killer; P: para; PP: postpartum; R-CHOP: rituximab: cyclophosphamide: doxorubicin: vincristine: prednisolone; RTX: rituximab; sCD25: soluble CD25; sIL-2R: soluble interleukin-2 receptor; SLE: systemic lupus erythematosus; TOP: termination of pregnancy; TG: triglycerides; VD: vaginal delivery.

Table 3. HLH-2004 diagnostic criteria (for use in non-pregnant individuals).[54]

HLH-2004 diagnostic criteria (≥5 of 8 criteria below)
1. Fever
2. Splenomegaly
3. Cytopenia affecting ≥2 of 3 peripheral blood lineages
– Haemoglobin < 90 g/L
– Platelets < 100 ×10⁹/L
– Neutrophils <1.0 × 10⁹/L
4. Hypertriglyceridaemia and/or hypofibrinogenaemia
– Fasting triglycerides ≥3.0 mmol/L
– Fibrinogen ≤1.5 g/L
5. Haemophagocytosis in bone marrow, spleen or lymph nodes with no evidence of malignancy
6. Low or no NK cell activity
7. Ferritin ≥500 μg/L
8. Soluble CD25 (i.e. soluble interleukin-2 receptor, sIL-2R) ≥2400 U/ml

Table 4. HScore parameters and points.[55]

Parameter	Number of points	
Known underlying immunosuppression	No	0
	Yes	+18
Temperature (°C)	<38.4	0
	38.4–39.4	+33
	>39.4	+49
Organomegaly	No	0
	Hepatomegaly or splenomegaly	+23
	Hepatomegaly and splenomegaly	+38
Cytopenia lineage(s)	1	0
	2	+24
	3	+34
Ferritin (μg/L)	<2000	0
	2000–6000	+35
	>6000	+50
Triglyceride (mmol/L)	<1.5	0
	1.5 − 4	+44
	>4	+64
Fibrinogen (g/L)	>2.5	0
	≤2.5	+30
Aspartate aminotransferase (U/L)	<30	0
	≥30	+19
Haemophagocytosis on bone marrow aspirate	No	0
	Yes	+35

individual with sepsis not responding to conventional antimicrobials. Very elevated ferritin levels and progressive cytopenia (particularly reduction in platelet count) can be signs of evolving HLH and are useful markers in this context.[54]

Initial investigations should be tailored to the diagnostic criteria listed in Table 3 and include full blood count, blood film, coagulation screen (including fibrinogen) and erythrocyte sedimentation rate (ESR). ESR is affected by pregnancy but, like many investigations in HLH, single measurements are unhelpful but trends of measurements over days can be enlightening. A high ESR due to infection or pregnancy will fall due to fibrinogen consumption as HLH evolves.[65] Anaemia is common in pregnancy due to fetal demand for iron and haemodilution.[57] However, the downward haemoglobin trend is much more marked in evolving sHLH in pregnancy, and the blood film often reveals concomitant thrombocytopenia. Microcytic hypochromic red cells and characteristic pencil cells of iron deficiency may also be observed, but these are not accompanied by low ferritin levels in sHLH. Fibrinogen is classically low due to consumption in HLH and raised in infection. Thus, daily haematology tests are required to create trends to guide the suspecting clinician.

Biochemistry to assess for end-organ damage (renal profile and hepatic function), ferritin, lipids (including triglycerides), lactate dehydrogenase (LDH), C-reactive protein (CRP) and haematinics should also be performed and repeated regularly. sCD25 should be sent in all cases, but the results typically take many weeks and do not currently assist in the immediate diagnostic phase unless in a specialist centre. Genetic testing for pHLH genotypes should be considered in all young adults, women with a family history, those with EBV-driven sHLH and also requested in those in whom no cause for their HLH can be identified.

Further investigations should be geared towards elucidating the underlying aetiology. Bacterial blood cultures should be taken alongside serum for EBV and CMV serology and PCR, viral hepatitis screen for Hepatitis A, B and C, human immunodeficiency viruses (HIV) and Parvovirus B19. Given the higher prevalence of autoimmunity in women of childbearing age, we advocate the testing of antinuclear antibodies (ANA), extractable nuclear antigens (ENA), antineutrophil cytoplasmic antibodies (ANCA), complement (C3 and C4) and double-stranded DNA (dsDNA) levels in all cases.

Bone marrow examination should be performed in all cases, where possible, as it will not only confirm the presence of haemophagocytic activity but aid in the diagnosis of underlying haematological malignancies as the driver for the disease. The presence of haemophagocytosis in the bone marrow is not, however, diagnostic for HLH; it can be seen in other settings such as after blood transfusion and chemotherapy, in fulminant sepsis, and after surgery.[66] The absence of haemophagocytosis on the marrow examination does also not exclude the diagnosis, if clinical suspicion and other markers are supportive.[5] A few small studies have investigated the quantification of haemophagocytosis in the marrow and its correlation with the eventual diagnosis of HLH. A case-control study, using aspirates only, showed the extent of haemophagocytosis to be higher in those with HLH with a sensitivity of 83% and a specificity of 60%.[67] A larger blinded retrospective study evaluating 64 bone marrow aspirates and core biopsy specimens from adult women with a clinical phenotype suspicious for sHLH revealed no correlation between the amount of haemophagocytosis observed and clinical disease.[66]

Often imaging may be required in the diagnostic work-up. Magnetic resonance imaging (MRI) of the brain and culture of cerebrospinal fluid may be appropriate in the context of neurological involvement, while cross-sectional imaging using computerised and/or positron-emission tomography followed by targeted lymph node or solid organ biopsy can identify malignancy. The use of imaging techniques involving ionising radiation may be appropriate in pregnancy but should be discussed in a multidisciplinary team (MDT), and alternatives considered.

A suspected diagnosis of sHLH in pregnancy should be urgently discussed with a regional expert or in a specialist multidisciplinary team (MDT) HLH meeting, as the complexities of treatment may require the need for early specialist transfer if it safe to do so given the associated high mortality.

Treatment

The treatment of sHLH typically involves management of the underlying cause, which may not be easily identified. In the interim, empirical immunosuppressive treatment based is generally advocated in order to rapidly suppress the hyperinflammation and buy time to identify the underlying trigger, allowing for more targeted definitive
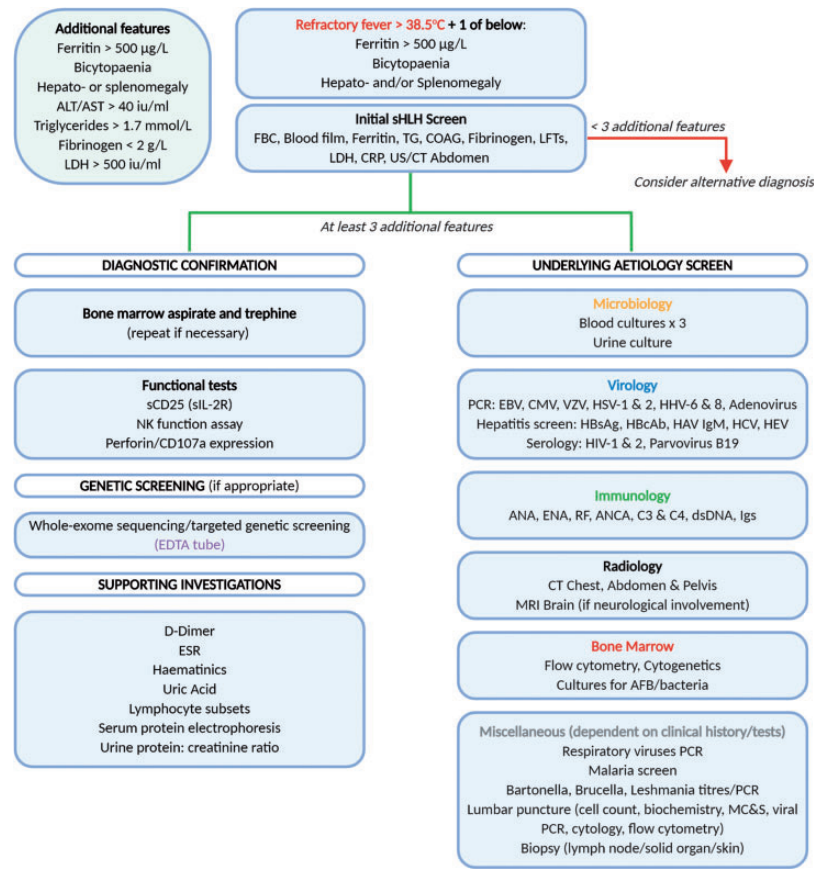
Figure 2. Proposed algorithm for investigation of suspected HLH in pregnancy. AFB: acid-fast bacillus; ALT: alanine aminotransferase; ANA: antinuclear antibody; ANCA: anti-neutrophil cytoplasmic antibody; AST: aspartate aminotransferase; C: complement; CMV: cytomegalovirus; COAG: coagulation studies; CRP: c-reactive protein; CT: computerised tomography; dsDNA: double-stranded DNA; EBV: Epstein-Barr virus: ENA: extractable nuclear antigen; ESR: erythrocyte sedimentation rate; FBC: full blood count; HAV IgM: hepatitis A immunoglobulin M; HBcAb: hepatitis B core antibody; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HEV: hepatitis E virus; HHV: human herpesvirus; HIV: human immunodeficiency virus; HSV: herpes simplex virus; Igs: immunoglobulins; LDH: lactate dehydrogenase; LFTs: liver function tests; MC&S: microscopy culture and sensitivity; MRI: magnetic resonance imaging; NK: natural killer; PCR: polymerase chain reaction; RF: rheumatoid factor; sCD25: soluble CD25; sIL-2R: soluble interleukin-2 receptor; TG: triglyceride; US: ultrasound.

treatment of the underlying aetiological driver. Delivery must be considered in each case of HLH in pregnancy and has been shown to lead to rapid clinical and biochemical resolution in some cases.[28]

Typically, glucocorticoids and intravenous immunoglobulin are used to rapidly suppress the acute phase response and to allow time for diagnostic investigations to both confirm the clinical suspicion of HLH and look for the underlying aetiology. The widely used paediatric HLH-94 protocol includes the use of high-dose dexamethasone, the topoisomerase II inhibiting alkylating agent etoposide, the calcineurin inhibitor ciclosporin A (CsA) and employs intrathecal methotrexate in cases with central nervous system involvement.[68] However, this is not necessary in many cases of sHLH where immunosuppression and treatment of the underlying driver of the HLH can lead to resolution. In the last decade, the use of targeted cytokine inhibition has been introduced to the management of HLH, and can lead to a rapid clinical response.[69]

Non-selective immunosuppressive agents

Glucocorticoids. Glucocorticoids mediate anti-inflammatory effects on both genomic and non-genomic levels when bound to the intracellular glucocorticoid receptor (GR). Classically, high-dose glucocorticoids such as intravenous methylprednisolone or dexamethasone are used; the latter has greater anti-macrophage activity and is the glucocorticoid of choice in this condition. Furthermore, dexamethasone has particular use in the context of neurological involvement as it has the capacity to permeate across the blood–brain barrier, but dose-related caution should be implemented to avoid CNS toxicity.[70] Methylprednisolone is often preferred in pregnancy due to reduced placental transfer compared to dexamethasone, and is therefore the glucocorticoid if no clear CNS involvement.

In cases where the underlying sHLH trigger has been elusive, high-dose steroid use can blur the diagnostic picture. As aforementioned, a common driver of sHLH is lymphoproliferative disease, which can be exquisitely sensitive to glucocorticoids. Therefore, their early use in sHLH cases may obviate the swift diagnosis of lymphoma resulting in additional investigations and the need for repeat sampling once disease-masking doses have been weaned.

Intravenous immunoglobulin. The use of intravenous immunoglobulin (IVIg) is safe and in combination with glucocorticoids forms the backbone of some HLH treatment regimens. Like many

interventions in sHLH, however, evidence is lacking.[71,72] It achieves its anti-inflammatory effects by competitively binding to the Fc-receptor on macrophages, causing downstream modulation of B- and T-cell activity, and inhibiting complement activation.[73] Clinical experience over many years of its use for the treatment of autoimmune conditions in pregnancy does not suggest any harmful effect to the developing fetus, nor the infant during breastfeeding.[74] IVIg is expensive, however, and supplies can be restricted.

Corticosteroids and IVIg are both used in the management of pregnancy-associated sHLH, but their combined use is not always enough to induce remission.[14,75]

Selective immunosuppressive agents

Calcineurin inhibitors. Ciclosporin A (CsA) is a calcineurin inhibitor that binds to the receptor cyclophilin-1 leading to downstream effects that inhibit the transcription of key inflammatory cytokines, such as IL-2. This leads to the downregulation of activated T-cells.[76] CsA has been used in severe cases of pregnancy-associated sHLH refractory to corticosteroids with varying results.[23,40] It has been seen to be most effective in sHLH secondary to autoimmune disease.[2] Often in these cases there is a suboptimal response to corticosteroids alone, and CsA is used as a potent adjunct to first-line therapy. Its early introduction in those treated with HLH-94 etoposide-dexamethasone based regimens did not improve outcomes, however.[71]

CsA has a favourable safety profile in pregnancy derived from long-term solid organ transplant data.[77] Prematurity and intrauterine growth restriction (IUGR) leading to low infant birthweights have been reported but CsA does not appear to be a human teratogen.[77] Long-term data are still required to consolidate its safety during breastfeeding, but there are no reports of adverse effects on growth, development or renal function despite varying recorded levels of CsA in breast milk.[78]

Cytokine inhibitors

Anakinra. Anakinra, a recombinant IL-1 receptor antagonist (IL-1Ra), has become favoured in recent years due to its excellent safety profile, rapid onset of action and its short half-life.[79] It provides a physiological steroid-sparing path to IL-1 downregulation resulting in additional time for further investigation of the underlying aetiology.[80] Anakinra requires daily dosing and can be administered either via subcutaneous or intravenous routes. Fewer than 50 cases of anakinra use in pregnancy have been reported.[81–84] The majority completed successful pregnancies to term with normal neonatal checks. One case of fetal unilateral hearing loss and two cases of renal agenesis have been reported. A causal link between anakinra and renal agenesis is uncertain as in both cases there was maternal illness (uncontrolled inflammation in one case and the other a twin pregnancy in a woman with autoimmune disease and glucocorticoid-induced diabetes mellitus).[85] Anakinra is considered appropriate to use in pregnancy, and no concerns have been identified with its ongoing use in breastfeeding in a large international multicentre study.[86]

Tocilizumab. Tocilizumab (TCZ) is a monoclonal antibody that targets the receptor of IL-6. It is widely used in systemic-onset juvenile arthritis and adult-onset Still's disease which can lead to sHLH.[69] By inhibiting IL-6, TCZ effectively abrogates the acute phase response leading to normalisation of measurable parameters of inflammation and infection such as fever, CRP and ferritin but is not necessarily synonymous with disease control.[87]

There are currently no controlled studies of TCZ use in human pregnancy; the current literature of 360 exposed pregnancies demonstrates cases of congenital anomaly, miscarriage, preterm delivery

and low birth weight, seen at a similar incidence when compared to rates in the unexposed pregnant population.[88]

Etoposide. Etoposide is a chemotherapeutic drug primarily used in cancer treatment. It selectively inhibits topoisomerase II preventing re-ligation of DNA strands leading to acquired errors in DNA synthesis and apoptosis of cancer cells. Etoposide selectively induces apoptosis of activated T-cells leading to a marked reduction in inflammatory cytokine production while sparing memory T-cells.[89] The HLH-94 paediatric treatment protocol contains etoposide as a key component, and its adapted use in adults, extrapolated from this, is often effective at reversing the life-threatening sequelae of sHLH.[71] Dose reduction is advised if renal impairment is present, as etoposide is primarily renally excreted.[90] Etoposide's potential toxicity to the fetus is an obvious concern in the treatment of sHLH in pregnancy. Although there is no statistically significant increase in the number of congenital malformations seen in pregnancies exposed to chemotherapy after the first trimester,[91] etoposide use after this time has been seen to result in adverse fetal ovarian development in mice studies.[92] However, the clinical scenario may warrant the use of the drug in pregnant women despite potential risks although delivery would have to be strongly considered.[93]

Emapalumab. Emapalumab is a fully human immunoglobulin G1 monoclonal antibody directed against IFN-γ developed for use in HLH. Favourable outcomes have been observed in paediatric cases of refractory pHLH.[94] A phase 2/3 interventional study (NCT03985423) is currently recruiting adult women to assess the efficacy, safety and pharmacokinetics of emapalumab in sHLH, but severe infections have been noted in the existing data.[95] No data exist relating to the use of emapalumab in the context of pregnancy and breastfeeding in humans.[96]

Ruxolitinib. Ruxolitinib is a selective inhibitor of the Janus-associated tyrosine kinases JAK1 and JAK2, whose role in the JAK/STAT signalling pathway contributes to the cytokine-mediated hyperinflammatory state seen in sHLH.[97] It is used in the treatment of myeloproliferative neoplasms such as myelofibrosis and polycythaemia vera, but promising results in the context of adult HLH have been observed in pre-clinical trials and case series.[97,98] A phase 2 interventional study (NCT02400463) is currently recruiting adult women to assess efficacy and safety of ruxolitinib in sHLH and the preliminary data are encouraging in both regards.[99] There are no current data for its use in the context of pregnancy. Tofacitinib, another JAK inhibitor used in the treatment of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis, has been shown to be teratogenic in rats, thus its use in pregnancy is currently largely contraindicated despite a human study revealing adverse rates comparable to the unexposed background risk.[100,101]

B-cell depletion

Rituximab. There are known triggers for sHLH in pregnancy where the use of rituximab, a genetically engineered chimeric murine/human monoclonal antibody that targets CD20, may be indicated. Typically, it is used in conjunction with glucocorticoids and IVIg (and cytokine inhibitors) in the treatment of sHLH due to B-cell lymphoma, severe systemic lupus erythematosus and in EBV-driven HLH where rituximab is used repeatedly to deplete the B-cells in which the virus is actively replicating.[37]

Rituximab use in pregnancy can lead to B-cell depletion in the fetus if given beyond 16 weeks of gestation, increasing the potential risks of neonatal infection.[102] Congenital abnormalities have also been reported; however, its use is generally considered acceptable if

indicated in a pregnant woman with sHLH, and other conditions where there are no suitable alternative options.[103]

Transplantation

Haematopoietic stem cell transplantation (HSCT) is established for pHLH and refractory sHLH including those occurring in pregnancy but only performed postpartum. Successful outcomes have been reported after delivery and focused chemotherapy.[24] Despite the commonly reported occurrence of HSCT-related infertility, women are able to retain or recover fertility and conceive.[104]

Delivery

Maternal and fetal outcomes following delivery in reported cases of HLH in pregnancy are mixed (Table 2). Emergency caesarean sections were performed in cases where fetal complications were observed, but they were more frequently undertaken to aid maternal treatment and complete remission was occasionally achieved after delivery.[28,45,47] This raises a key question – does early delivery lead to better outcomes? This has yet to be proven and so delivery is not mandated when the diagnosis is made, but close monitoring of mother and fetus is required, and delivery performed if the mother's condition is deteriorating, or if there is evidence of fetal compromise.[9]

Future pregnancies

Future pregnancies for any woman following HLH in pregnancy should be carefully considered and planned. If there was a clear and transient trigger for the sHLH in pregnancy, such as infection, there is no suggestion that subsequent pregnancies will lead to recurrence; however, caution is advised. A caveat to this is if the infection is triggered by EBV, genetic testing for underlying primary HLH is strongly advised. For those with autoimmune disease such as SLE, which may have presented as sHLH in pregnancy, future pregnancies should be carefully planned, taking place following adequate disease control and on non-teratogenic treatment regimens. If the cause for sHLH in pregnancy was not identified, we suggest genetic testing and referral to a specialist HLH centre for investigation prior to the planning of subsequent pregnancies.

Conclusion

HLH in pregnancy is a rare, but likely underdiagnosed, subtype of a complex life-threatening multisystem inflammatory syndrome. It provides significant diagnostic challenges due to its spectrum of underlying aetiologies and the subsequent diagnostic delay contributes to the high mortality seen. Serum ferritin measurement can hint at the diagnosis of sHLH in pregnancy and trigger further investigation and involvement of specialists early in the disease course. The use of immunosuppression and more targeted therapies presents more efficacious and less toxic treatment options. The interleukin-1 receptor antagonist, anakinra, is particularly attractive in this setting due to its established efficacy and physiological nature, but more importantly its short half-life lends itself well to use in hyperinflammation triggered by infection. Refractory cases may require difficult decisions to be made regarding delivery and the use of more toxic treatment regimens. Future pregnancies need to be carefully considered in the context of the underlying aetiology of the HLH. Particularly, caution should be taken in those in whom an aetiological trigger has not been identified.

ORCID iD

Taryn Youngstein https://orcid.org/0000-0002-8297-556X

References

1. Grom AA. Macrophage activation syndrome and reactive hemophagocytic lymphohistiocytosis: the same entities? *Curr Opin Rheumatol* 2003; 15: 587–590.
2. La Rosee P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood* 2019; 133: 2465–2477.
3. Grom AA. Natural killer cell dysfunction: a common pathway in systemic-onset juvenile rheumatoid arthritis, macrophage activation syndrome, and hemophagocytic lymphohistiocytosis? *Arthritis Rheum* 2004; 50: 689–698.
4. Machowicz R, Janka G and Wiktor-Jedrzejczak W. Similar but not the same: differential diagnosis of HLH and sepsis. *Crit Rev Oncol Hematol* 2017; 114: 1–12.
5. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, et al. Adult haemophagocytic syndrome. *Lancet* 2014; 383: 1503–1516.
6. Arca M, Fardet L, Galicier L, et al. Prognostic factors of early death in a cohort of 162 adult haemophagocytic syndrome: impact of triggering disease and early treatment with etoposide. *Br J Haematol* 2015; 168: 63–68.
7. Park HS, Kim DY, Lee JH, et al. Clinical features of adult patients with secondary hemophagocytic lymphohistiocytosis from causes other than lymphoma: an analysis of treatment outcome and prognostic factors. *Ann Hematol* 2012; 91: 897–904.
8. HistioUK. Histio UK Haemophagocytosis across specialty collaboration (HASC) initiative, www.histiocytosisuk.org/histio-uk-haemophagocytosis-across-specialty-collaboration-hasc-initiative/ (2020, accessed 12 April 2021).
9. Knight M, Nelson-Piercy C and Group Obotmasc W. Lessons for the care of women with medical and general surgical disorders. In: M Knight, M Nair, D Tuffnell, et al. (eds) *Saving lives, improving mothers' care – lessons learned to inform maternity care from the UK and Ireland confidential enquiries into maternal deaths and morbidity 2013–15*. Oxford:

National Perinatal Epidemiology Unit: University of Oxford, 2017, p. 55.

10. Janka GE and Lehmberg K. Hemophagocytic lymphohistiocytosis: pathogenesis and treatment. *Hematology Am Soc Hematol Educ Program* 2013; 2013: 605–611.

11. Zhang K, Jordan MB, Marsh RA, et al. Hypomorphic mutations in PRF1, MUNC13-4, and STXBP2 are associated with adult-onset familial HLH. *Blood* 2011; 118: 5794–5798.

12. Koch CA and Platt JL. Natural mechanisms for evading graft rejection: the fetus as an allograft. *Springer Semin Immunopathol* 2003; 25: 95–117.

13. Redman CW and Sargent IL. Pre-eclampsia, the placenta and the maternal systemic inflammatory response – a review. *Placenta* 2003; 24(Suppl A): S21–27.

14. Parrott J, Shilling A, Male HJ, et al. Hemophagocytic lymphohistiocytosis in pregnancy: a case series and review of the current literature. *Case Rep Obstet Gynecol* 2019; 2019: 9695367.

15. Zhang Z, Wang J, Ji B, et al. Clinical presentation of hemophagocytic lymphohistiocytosis in adults is less typical than in children. *Clinics* 2016; 71: 205–209.

16. Gill DS, Spencer A and Cobcroft RG. High-dose gammaglobulin therapy in the reactive haemophagocytic syndrome. *Br J Haematol* 1994; 88: 204–206.

17. Tsuda H, Shirono K, Shimizu K, et al. Post-partum parvovirus B19-associated acute pure red cell aplasia and haemophagocytic syndrome. *Rinsho Ketsueki* 1995; 36: 672–676.

18. Yamanaka S, Katsube Y, Honda H, et al. A case of pregnancy complicated with virus-associated hemophagocytic syndrome. *Nihon Sanka Fujinka Gakkai Zasshi* 1995; 47: 503–506.

19. Ishida A, Matsumoto J, Kobayashi S, et al. [A case of reactive hemophagocytic syndrome which occurred during treatment of hyoeremesis]. *Kanto J Obstet Gynaecol* 1996; 33: 51–54.

20. Mihara H, Kato Y, Tokura Y, et al. Epstein-Barr virus-associated hemophagocytic syndrome during mid-term pregnancy successfully treated with combined methylprednisolone and intravenous immunoglobulin. *Rinsho Ketsueki* 1999; 40: 1258–1264.

21. Nakabayashi M, Adachi T, Izuchi S, et al. Association of hypercytokinemia in the development of severe preeclampsia in a case of hemophagocytic syndrome. *Semin Thromb Hemost* 1999; 25: 467–471.

22. Chmait R, Meimin D, Koo C, et al. Hemophagocytic syndrome in pregnancy. *Obstet Gynecol* 2000; 95: 1022–1024.

23. Yamaguchi K, Yamamoto A, Hisano M, et al. Herpes simplex virus 2-associated hemophagocytic lymphohistiocytosis in a pregnant patient. *Obstet Gynecol* 2005; 105: 1241–1244.

24. Hanaoka M, Tsukimori K, Hojo S, et al. B-cell lymphoma during pregnancy associated with hemophagocytic syndrome and placental involvement. *Clin Lymphoma Myeloma* 2007; 7: 486–490.

25. Perard L, Costedoat-Chalumeau N, Limal N, et al. Hemophagocytic syndrome in a pregnant patient with systemic lupus erythematosus, complicated with preeclampsia and cerebral hemorrhage. *Ann Hematol* 2007; 86: 541–544.

26. Gonzalez E, Olvera H, Gonzalez V, et al. Hemophogocytic syndrome secondary to an infection with parvovirus B19. *Rev Chil Obstet Ginecol* 2008; 73: 406–410.

27. Chien CT, Lee FJ, Luk HN, et al. Anesthetic management for cesarean delivery in a parturient with exacerbated hemophagocytic syndrome. *Int J Obstet Anesth* 2009; 18: 413–416.

28. Teng C-L, Hwang G-Y, Lee B-J, et al. Pregnancy-induced hemophagocytic lymphohistiocytosis combined with autoimmune hemolytic anemia. *J Chin Med Assoc* 2009; 72: 156–159.

29. Yoshida S, Takeuchi T, Itami Y, et al. Hemophagocytic syndrome as primary manifestation in a patient with systemic lupus erythematosus after parturition. *Nihon Rinsho Meneki Gakkai Kaishi* 2009; 32: 66–70.

30. Arewa OP and Ajadi AA. Human immunodeficiency virus associated with haemophagocytic syndrome in pregnancy: a case report. *West Afr J Med* 2011; 30: 66–68.

31. Dunn T, Cho M, Medeiros B, et al. Hemophagocytic lymphohistiocytosis in pregnancy: a case report and review of treatment options. *Hematology* 2012; 17: 325–328.

32. Hannebicque-Montaigne K, Le Roc'h A, Launay D, et al. [Haemophagocytic syndrome in pregnancy: a case report]. *Ann Fr Anesth Reanim* 2012; 31: 239–242.

33. Kim JM, Kwok SK, Ju JH, et al. Macrophage activation syndrome resistant to medical therapy in a patient with systemic lupus erythematosus and its remission with splenectomy. *Rheumatol Int* 2013; 33: 767–771.

34. Komaru Y, Higuchi T, Koyamada R, et al. Primary Sjogren syndrome presenting with hemolytic anemia and pure red cell aplasia following delivery due to Coombs-negative autoimmune hemolytic anemia and hemophagocytosis. *Intern Med* 2013; 52: 2343–2346.

35. Shukla A, Kaur A and Hira HS. Pregnancy induced haemophagocytic syndrome. *J Obstet Gynaecol India* 2013; 63: 203–205.

36. Goulding EA and Barnden KR. Disseminated herpes simplex virus manifesting as pyrexia and cervicitis and leading to reactive hemophagocytic syndrome in pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2014; 180: 198–199.

37. Klein S, Schmidt C, La Rosee P, et al. Fulminant gastrointestinal bleeding caused by EBV-triggered hemophagocytic lymphohistiocytosis: report of a case. *Z Gastroenterol* 2014; 52: 354–359.

38. Mayama M, Yoshihara M, Kokabu T, et al. Hemophagocytic lymphohistiocytosis associated with a parvovirus B19 infection during pregnancy. *Obstet Gynecol* 2014; 124: 438–441.

39. Samra B, Yasmin M, Arnaout S, et al. Idiopathic hemophagocytic lymphohistiocytosis during pregnancy treated with steroids. *Hematol Rep* 2015; 7: 6100.

40. Tumian NR and Wong CL. Pregnancy-related hemophagocytic lymphohistiocytosis associated with cytomegalovirus infection: a diagnostic and therapeutic challenge. *Taiwan J Obstet Gynecol* 2015; 54: 432–437.

41. Giard JM, Decker KA, Lai JC, et al. Liver failure secondary to hemophagocytic lymphohistiocytosis during pregnancy. *ACG Case Rep J* 2016; 3: e162.

42. Ota K, Kawahara K, Banno H, et al. Hemophagocytic lymphohistiocytosis caused by pyogenic liver abscess during pregnancy: a case report and literature review. *Open J Obstet Gynecol* 2016; 06: 287–292.

43. He M, Jia J, Zhang J, et al. Pregnancy-associated hemophagocytic lymphohistiocytosis secondary to NK/T cells lymphoma: a case report and literature review. *Medicine* 2017; 96: e8628.

44. Ikeda M, Oba R, Yoshiki Y, et al. Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis during pregnancy. *Rinsho Ketsueki* 2017; 58: 216–221.

45. Kerley RN, Kelly RM, Cahill MR, et al. Haemophagocytic lymphohistiocytosis presenting as HELLP syndrome: a diagnostic and therapeutic challenge. *BMJ Case Rep* 2017; 2017: doi:10.1136/bcr-2017-219516.

46. Rousselin A, Alavi Z, Le Moigne E, et al. Hemophagocytic syndrome in pregnancy: case report, diagnosis, treatment, and prognosis. *Clin Case Rep* 2017; 5: 1756–1764.

47. Nasser MF, Sharma S, Albers E, et al. Pregnancy-related hemophagocytic lymphohistiocytosis associated with herpes simplex virus-2 infection: a diagnostic dilemma. *Cureus* 2018; 10: e2352.

48. Cheng J, Niu J, Wang Y, et al. Hemophagocytic lymphohistiocytosis in pregnancy: a case report and review of the literature. *J Obstet Gynaecol* 2020; 40: 153–159.

49. Yip KP, Ali M, Avann F, et al. Pregnancy-induced haemophagocytic lymphohistiocytosis. *J Intensive Care Soc* 2020; 21: 87–91.

50. de Kerguenec C, Hillaire S, Molinie V, et al. Hepatic manifestations of hemophagocytic syndrome: a study of 30 cases. *Am J Gastroenterol* 2001; 96: 852–857.

51. Rosado FG and Kim AS. Hemophagocytic lymphohistiocytosis: an update on diagnosis and pathogenesis. *Am J Clin Pathol* 2013; 139: 713–727.

52. Horne A, Trottestam H, Arico M, et al. Frequency and spectrum of central nervous system involvement in 193 children with haemophagocytic lymphohistiocytosis. *Br J Haematol* 2008; 140: 327–335.

53. Seguin A, Galicier L, Boutboul D, et al. Pulmonary involvement in patients with hemophagocytic lymphohistiocytosis. *Chest* 2016; 149: 1294–1301.

54. Henter JI, Horne A, Arico M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007; 48: 124–131.

55. Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol* 2014; 66: 2613–2620.

56. Naymagon L. Can we truly diagnose adult secondary hemophagocytic lymphohistiocytosis (HLH)? A critical review of current paradigms. *Pathol Res Pract* 2021; 218: 153321.

57. Pavord S, Myers B, Robinson S, et al. UK guidelines on the management of iron deficiency in pregnancy. *Br J Haematol* 2012; 156: 588–600.

58. Wang W, Knovich MA, Coffman LG, et al. Serum ferritin: past, present and future. *Biochim Biophys Acta* 2010; 1800: 760–769.

59. Abbassi-Ghanavati M, Greer LG and Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. *Obstet Gynecol* 2009; 114: 1326–1331.

60. Asif N, Hassan K, Mahmud S, et al. Comparison of serum ferritin levels in three trimesters of pregnancy and their correlation with increasing gravidity. *Int J Pathol* 2007; 5: 26–30.

61. Allen CE, Yu X, Kozinetz CA, et al. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2008; 50: 1227–1235.

62. Schram AM, Campigotto F, Mullally A, et al. Marked hyperferritinemia does not predict for HLH in the adult population. *Blood* 2015; 125: 1548–1552.

63. Hayden A, Lin M, Park S, et al. Soluble interleukin-2 receptor is a sensitive diagnostic test in adult HLH. *Blood Adv* 2017; 1: 2529–2534.

64. Naymagon L, Tremblay D, Troy K, et al. Soluble interleukin-2 receptor (sIL-2r) level is a limited test for the diagnosis of adult secondary hemophagocytic lymphohistiocytosis. *Eur J Haematol* 2020; 105: 255–261.

65. Schram AM and Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. *Blood* 2015; 125: 2908–2914.

66. Ho C, Yao X, Tian L, et al. Marrow assessment for hemophagocytic lymphohistiocytosis demonstrates poor correlation with disease probability. *Am J Clin Pathol* 2014; 141: 62–71.

67. Goel S, Polski JM and Imran H. Sensitivity and specificity of bone marrow haemophagocytosis in haemophagocytic lymphohistiocytosis. *Ann Clin Lab Sci* 2012; 42: 21–25.

68. Trottestam H, Horne A, Arico M, et al. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. *Blood* 2011; 118: 4577–4584.

69. Carter SJ, Tattersall RS and Ramanan AV. Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment. *Rheumatology* 2019; 58: 5–17.

70. Ciriaco M, Ventrice P, Russo G, et al. Corticosteroid-related central nervous system side effects. *J Pharmacol Pharmacother* 2013; 4: S94–98.

71. Bergsten E, Horne A, Arico M, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. *Blood* 2017; 130: 2728–2738.

72. Dunogue B, Gerin M, Larroche C, et al. Intravenous immunoglobulin therapy for secondary hemophagocytic lymphohistiocytosis: a retrospective study of 46 patients. *ACR/ARHP Ann Meet* 2014; 2199, https://acrabstracts.org/abstract/intravenous-immunoglobulin-therapy-for-secondary-hemophagocytic-lymphohistiocytosis-a-retrospective-study-of-46-patients/.

73. Bayry J, Lacroix-Desmazes S, Kazatchkine MD, et al. Monoclonal antibody and intravenous immunoglobulin therapy for rheumatic diseases: rationale and mechanisms of action. *Nat Clin Pract Rheumatol* 2007; 3: 262–272.

74. Ferrero S, Esposito F, Pretta S, et al. Fetal risks related to the treatment of multiple sclerosis during pregnancy and breastfeeding. *Expert Rev Neurother* 2006; 6: 1823–1831.

75. Song Y, Wang Z, Hao Z, et al. Requirement for etoposide in the treatment of pregnancy related hemophagocytic lymphohistiocytosis: a multicenter retrospective study. *Orphanet J Rare Dis* 2019; 14: 50.

76. Russell G, Graveley R, Seid J, et al. Mechanisms of action of cyclosporine and effects on connective tissues. *Semin Arthritis Rheum* 1992; 21: 16–22.

77. Paziana K, Del Monaco M, Cardonick E, et al. Ciclosporin use during pregnancy. *Drug Saf* 2013; 36: 279–294.

78. Constantinescu S, Pai A, Coscia LA, et al. Breast-feeding after transplantation. *Best Pract Res Clin Obstet Gynaecol* 2014; 28: 1163–1173.

79. Opal SM, Fisher CJ, Jr., Dhainaut JF, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. *Crit Care Med* 1997; 25: 1115–1124.

80. Shabbir S, Al-Abdulla A, Kinderlerer A, et al. THU0051 off-licence use of anakinra in critically ill adults with suspected haemophagocytosis – a single centre experience. *Ann Rheum Dis* 2019; 78: 292–293.

81. Lachmann HJ, Ozdogan H, Simon A, et al. OR14-002 – ANTI IL-1 therapies and pregnancy outcome. *Pediatr Rheumatol* 2013; 11: A269.

82. Ilgen U and Kucuksahin O. Anakinra use during pregnancy: report of a case with familial Mediterranean fever and infertility. *Eur J Rheumatol* 2017; 4: 66–67.

83. Venhoff N, Voll RE, Glaser C, et al. IL-1-blockade with Anakinra during pregnancy: retrospective analysis of efficacy and safety in female patients with familial Mediterranean fever. *Z Rheumatol* 2018; 77: 127–134.

84. Chang Z, Spong CY, Jesus AA, et al. Anakinra use during pregnancy in patients with cryopyrin-associated periodic syndromes (CAPS). *Arthritis Rheumatol* 2014; 66: 3227–3232.

85. Rider RA, Stevenson DA, Rinsky JE, et al. Association of twinning and maternal age with major structural birth defects in

Utah, 1999 to 2008. *Birth Defects Res A Clin Mol Teratol* 2013; 97: 554–563.

86. Youngstein T, Hoffmann P, Gul A, et al. International multi-centre study of pregnancy outcomes with interleukin-1 inhibitors. *Rheumatology* 2017; 56: 2102–2108.

87. Shimizu M, Nakagishi Y, Kasai K, et al. Tocilizumab masks the clinical symptoms of systemic juvenile idiopathic arthritis-associated macrophage activation syndrome: the diagnostic significance of interleukin-18 and interleukin-6. *Cytokine* 2012; 58: 287–294.

88. UKTIS. Use of tocilizumab in pregnancy, www.medicinesinpregnancy.org/bumps/monographs/USE-OF-TOCILIZUMAB-IN-PREGNANCY/ (2020, accessed 12 April 2021).

89. Johnson TS, Terrell CE, Millen SH, et al. Etoposide selectively ablates activated T cells to control the immunoregulatory disorder hemophagocytic lymphohistiocytosis. *J Immunol* 2014; 192: 84–91.

90. Ehl S, Astigarraga I, von Bahr Greenwood T, et al. Recommendations for the use of etoposide-based therapy and bone marrow transplantation for the treatment of HLH: consensus statements by the HLH steering committee of the histiocyte society. *J Allergy Clin Immunol Pract* 2018; 6: 1508–1517.

91. Cardonick E, Usmani A and Ghaffar S. Perinatal outcomes of a pregnancy complicated by cancer, including neonatal follow-up after in utero exposure to chemotherapy: results of an international registry. *Am J Clin Oncol* 2010; 33: 221–228.

92. Stefansdottir A, Johnston ZC, Powles-Glover N, et al. Etoposide damages female germ cells in the developing ovary. *BMC Cancer* 2016; 16: 482.

93. Inc CM. UK summary of product characteristics, www.drugs.com/pregnancy/etoposide.html#ref_pregnancy (2019, accessed 12 April 2021).

94. Locatelli F, Jordan MB, Allen C, et al. Emapalumab in children with primary hemophagocytic lymphohistiocytosis. *N Engl J Med* 2020; 382: 1811–1822.

95. Vallurupalli M and Berliner N. Emapalumab for the treatment of relapsed/refractory hemophagocytic lymphohistiocytosis. *Blood* 2019; 134: 1783–1786.

96. Sobi. Gamifant (emapalumab) prescribing information, www.accessdata.fda.gov/drugsatfda_docs/label/2018/761107lbl.pdf (2018, accessed 12 April 2021).

97. Goldsmith SR, Saif Ur Rehman S, Shirai CL, et al. Dramatic resolution of HLH after treatment with the JAK 1/2 inhibitor, *ruxolitinib Blood* 2019; 134: 2325.

98. Albeituni S, Verbist KC, Tedrick PE, et al. Mechanisms of action of ruxolitinib in murine models of hemophagocytic lymphohistiocytosis. *Blood* 2019; 134: 147–159.

99. Ahmed A, Merrill SA, Alsawah F, et al. Ruxolitinib in adult patients with secondary haemophagocytic lymphohistiocytosis: an open-label, single-centre, pilot trial. *Lancet Haematol* 2019; 6: e630e7.

100. Pfizer. Xeljanz (tofacitinib) prescribing information. 2018, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203214s018lbl.pdf.

101. Clowse ME, Feldman SR, Isaacs JD, et al. Pregnancy outcomes in the tofacitinib safety databases for rheumatoid arthritis and psoriasis. *Drug Saf* 2016; 39: 755–762.

102. Flint J, Panchal S, Hurrell A, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. *Rheumatology* 2016; 55: 1693–1697.

103. Chakravarty EF, Murray ER, Kelman A, et al. Pregnancy outcomes after maternal exposure to rituximab. *Blood* 2011; 117: 1499–1506.

104. Salooja N, Michonneau D, Tichelli A, et al. Conception and pregnancy outcomes after haematopoietic stem cell transplant: a retrospective study from the transplant complications working party of the European Society for Blood and Marrow Transplantation. *Blood* 2018; 132: 2139.