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Placenta derived factors involved in the pathogenesis of the liver in the syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP): A review

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ABSTRACT

Aim: With this review we try to unravel if placenta-derived factors are able to initiate liver sinusoidal endothelial cells (LSEC) decay in HELLP syndrome and eventually cause the development of sinusoidal obstruction syndrome (SOS).
Background: Haemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome is a severe complication of pregnancy. It is characterized by elevated liver enzymes, low platelet count and haemolytic anaemia. The risk of developing HELLP syndrome within a pregnancy is 0.1–0.8%. The mortality rate among women with HELLP syndrome is 0–24% and the perinatal death goes up to 37%. The aetiology of HELLP syndrome is not fully understood but the pathogenesis of the liver pathology in the HELLP syndrome resembles that of a SOS with endothelial damage of the LSECs which ultimately leads to liver failure.
Objectives: We hypothesize that placenta derived factors cause LSEC damage and thereby liver dysfunction.
Methods: We searched in the PubMed database for relevant articles about placenta derived factors involved in endothelial activation especially in the liver. We yielded eventually 55 relevant articles.
Results: Based on this literature search we associate that in HELLP syndrome there is an increase of soluble fms-like tyrosine kinase (sFlt1), vascular endothelial growth factor (VEGFR), soluble endoglin (sEng), galectin-1 (Gal-1), endothelin-1 (ET-1), Angiopoietin 2 (Angs-2), Asymmetric dimethylarginine (ADMA), activin B, inhibin A, Fas ligand (FasL) and heat shock protein 70 (Hsp70).
Conclusion: We assume that these eleven increased placenta derived factors are responsible for LSEC damage which eventually leads to liver failure. This concept shows a possible design of the complicated pathophysiology in HELLP syndrome. However further research is required.

1. Introduction

Haemolysis Elevated Liver Enzyme and Low Platelet (HELLP) syndrome is a severe complication of pregnancy. It is characterized by elevated liver enzymes, low platelet count and haemolytic anaemia [1]. HELLP syndrome occurs in 0.1–0.8% of the pregnancies and it coexists in 80% of the cases with pre-eclampsia, defined as hypertension and protein loss in the urine [2]. Patients develop HELLP syndrome usually before 36 weeks of gestation. Symptoms are malaise (90%), epigastric or right upper-quadrant pain (90%) and nausea or vomiting (50%) [3]. The only treatment at the moment is terminating the pregnancy. This gives a greater risk of having a premature baby. Premature babies have a higher morbidity and mortality rate. The overall perinatal mortality rate is 7–20 percent [3].

The exact aetiology of HELLP syndrome is not fully understood. It is thought to develop secondary to an inflammatory response in the placenta-liver axis. This pathway is primarily initiated in the placenta and then reaches the liver through the bloodstream, where it probably induces a form of sinusoidal obstruction syndrome (SOS). [non published article von Salmuth et al.]

Hepatic sinusoids represent the capillary bed of the liver and they have a diameter of 5–10 μm. Non-parenchymal liver cells separate

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hepatocytes from the bloodstream, by forming a thin layer of fenestrated liver sinusoidal endothelial cells (LSECs). Between the LSECs and the hepatocytes the small space of Disse is present. In the space of Disse there are stellate cells which functions as pericytes. Pericytes are contractile cells that are wrapped around the sinusoids. In the sinusoidal lumen there are Kupffer cells that functions as macrophages and lymphocytes including natural killer cells (NK cells), NK-T cells, naïve T-cells and B-cells. The fenestrated LSECs allow passive molecule exchange between the hepatocytes and the sinusoids in the liver. The fenestrations have an approximate diameter between 100–150 nm. They contribute to the regulation of sinusoidal blood flow, liver regeneration and hepatic complications [4].

In HELLP syndrome the pathophysiology mimics SOS as a result of an enhanced inflammatory state and endothelial damage caused by placental products and vasoactive substances. [non published article von Salmuth et al.] Endothelial damage in the liver in turn, may lead to red blood cells entering the space of Disse where they cause an obstruction. This leads to increased development of microthrombi and ischemia of the hepatocytes. This ultimately results in liver failure [1,5,6] [non published article von Salmuth et al.]. After delivery the hepatic function in HELLP patients usually returns to normal within 6 weeks. This causes us to primary focus on the placenta as an initiator of the pathophysiology from the liver [5].

In this review, we want to unravel the main placental derived factors in patients with HELLP syndrome. Further we investigate which possible mechanism of endothelial damage and activation of the inflammatory reaction in the liver causes the clinical course, considering the unique liver tissue structure of fenestrated sinusoidal endothelial cells within the space of Disse.

2. Methods

A literature search was performed with keywords 'Placenta derived factors', 'endothelial activation' and 'HELLP syndrome'. The search resulted in 568 potentially relevant articles. We performed an initial selection on titles and abstracts (See Fig. 1). We excluded 489 articles based on titles and abstracts because they were not written in English language, case reports, focussing on management of HELLP syndrome, focussing on outcome mother and/or child, epidemiology of HELLP syndrome, articles whose outcomes was not specifically based on HELLP syndrome. The potentially related articles were screened by full text, yielding 24 articles. We selected also 31 additional articles from the reference list from the articles we included for our review. This review was based on the information from the 55 articles we included. The final search was performed on November 3th,2017.

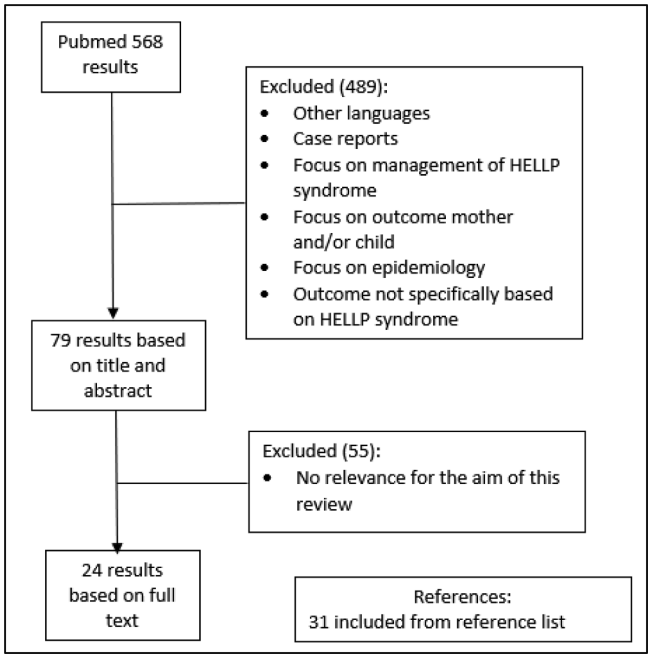

Fig. 1. Results of literature search.

3. Results

3.1. Factors involved in the pathophysiology of HELLP syndrome

It is thought that a dysfunctional placenta is the cause of HELLP syndrome. The dysfunctional placenta sheds factors in the bloodstream that cause the release of other factors and eventually reaches the liver where they induce malfunctioning.

In this review, we will evaluate the role of different factors increased in the sera of women with HELLP syndrome and the possible contribution of these factors in the pathophysiology of the liver in HELLP syndrome.

3.1.1. Factors influencing the vasculature

3.1.1.1. VEGF, sFlt-1 and sEng. The vascular endothelial growth factor (VEGF) is an important pro-angiogenic factor. It induces nitric oxide (NO) and prostacyclin release favouring vasodilatation. It is also necessary for the fenestration of endothelial cells and reduces the Endothelin-1 (ET-1) production from these cells [5,7,8]. VEGF concentration in sera of HELLP patients was significantly lower compared with serum VEGF concentrations of patients suffering from severe pre-eclampsia. Compared with the control group the VEGF concentration in HELLP patients and PE patients was significantly higher [9]. The expression in trophoblasts, in vessels and stromal cells was significantly higher in patients with HELLP syndrome compared with non pregnant controls. Compared with PE there was only a significant increase in VEGF expression in the vessels. In the HELLP group the placental mRNA levels were statistically lower compared with PE and normal controls [10]. Cytotrophoblast expression of VEGF and their receptors is down regulated in HELLP syndrome. Soluble vascular endothelial growth factor receptor-1 (sVEGFR-1) or also named soluble fms-like tyrosine kinase-1 (sFlt-1) secretion is increased in HELLP patients [11–15]. It acts as a potent VEGF and PlGF antagonist by preventing their interaction with their receptor. sFlt-1 is produced by the placenta, peripheral blood mononuclear cells, macrophages, endothelial cells and vascular smooth muscle cells [5]. Recently Whitehead and al. discovered a novel splice variant of sFlt (sFlt-e15a/sFlt-14). This splice variant was significantly upregulated in the placenta of women with PE and HELLP syndrome. There was a trend towards an increased expression of the novel variant in the placenta of women with HELLP syndrome compared with women suffering pre-eclampsia, but this did not meet statistical significance [13]. Endoglin is also a factor involved in the pathogenesis of HELLP syndrome. It is a coreceptor for transforming growth factor β1 and β3. This induces migration and proliferation of endothelial cells and it causes vasorelaxation [16]. Concentrations of soluble endoglin (sEng) were tenfold higher in individuals with HELLP syndrome compared with controls. Compared with PE the values of sEng are also higher in HELLP [1]. The concentrations of sEng were higher than that of sFlt1. sEng inhibited endothelial tube formation in the same extent as sFlt1. The combination of sEng and sFlt1 showed an effect on the liver, indicating that these soluble receptors may act in concert to disrupt endothelial integrity and induce considerable vascular damage and leak [1,15]. Proteinuria was modest in sEng-treated rats, but severe in the sFlt1-treated group. Liver histology showed signs of ischemia and areas of necrosis in the sFlt1 + sEng group, similar to individuals with HELLP syndrome. Evidence of hemolysis in the sFlt1 + sEng group was confirmed in peripheral blood smears [15]. sEng significantly attenuated the effects of TGF-β1 and TGF-β3. Endoglin is a coreceptor

for TGF-β1 and TGF-β3 isoforms and sEng acts by interfering with binding of cell-surface receptors. sEng significantly reduced binding of TGF-β1 to TGF-β receptor type II (TβRII) and thus competes for TGF-β1 binding to its receptors on endothelial cells [16]. TGF-β1 induces production of VEGF by the pericytes. sEng will probably interfere with VEGF functions through impaired production of VEGF by pericytes [17].

3.1.1.2. Gal-1. Galectin 1 (gal-1) is a homodimer that exist of two non-covalently associated subunits of approximately 130 amino acids with two carbohydrate recognition domains (CRDs). These CRDs recognize type I and type II N-acetyllactosamine residues present on all complex N-linked and O-linked glycoproteins [18]. Gal-1exerts important functions on immune modulation and angiogenesis by binding to neuropilin-1 (NRP-1) which enhance activation and signaling of VEGFR2. Gal-1 supplementation reduced sFlt-1, thereby enhancing VEGF bioavailability. It also increases the angiogenesis, matrix remodelling and modulates the migration of vascular endothelial cells [19]. Gal-1 is systemic significantly increased in patients with HELLP [20,21]. In the placenta is the expression in the syncytiotrophoblast significantly upregulated. In the extravillous trophoblast the gal-1 expression was upregulated in the cytosol. There is a significant negative correlation between the systemic gal-1 levels and platelets account in early-onset HELLP patients [20–22]. Gal-1 induces P-selectin and GPIIIa expression and triggers conformational changes in GPIIb/IIIa and F-actin polymerization on human platelets. These changes are dose-dependent. Gal-1 elicits Ca^{+2}-dependent mechanisms to modulate human platelet responses [21,23]. Ca^{2+}levels are elevated on platelet stimulation with Gal-1. Elevation of Ca^{2+} activates multiple signalling events, including thromboxane A2 (TXA_2) synthesis [23]. It promotes also generation of platelet-derived microparticles and microaggregates. The upregulation of p-selectin expression on the surface of activated platelets triggers multiple intracellular events in leukocytes and platelets that promote vascular inflammation and facilitate atherosclerosis and thrombotic episodes. When platelets are incubated PGI_2or NO before exposure to Gal-1 the shredding of microvesicles and P-selectin are prevented. Treatment with disaccharide lactose completely blocked the gal-1-induced P selectin and GPIIIa up-regulation [21].

3.1.1.3. ET-1. Endothelin 1 (ET-1) activates the ET pathway by binding the endothelin A receptor (ET_A) and mediates vasoconstriction, increases bloodpressure, contribute to oxidative stress, increases inflammatory cytokines and $CD4^+$T cells [24]. ET-1 is increased in plasma from HELLP patients. Circulating ET-1 was significantly increased in HELLP patients compared with PE and normal pregnant [24,25]. ET-1 is also increased in sera of PE patients but this was not significant compared to controls [25]. Endothelial cells produces significantly more ET-1 when exposed to sera from HELLP patients. Blockade of the ET_A receptor attenuates hypertension in HELLP rats. Hemolysis, liver enzymes, CD4+ and CD8+ cells are decreased and platelets are increased in HELLP rats treated with an ET_A antagonist. HELLP syndrome rats have higher blood-pressure, an increase in circulating ET-1, without a concomitant increase in placental or urinary secretion/excretion of ET-1 [24]. Inflammatory cytokines, agonistic autoantibodies to the angiotensin II type 1 receptor, increased sFlt1 and sEng are suggested to be mediators of ET-1 dysfunction. These factors are all increased in HELLP syndrome [26].

3.1.1.4. Angs-2. Angiopoietins are important modulators of angiogenesis and maintenance if vascular integrity. Angiopoietin-1 (Angs-1) and angiopoietin-2 (Angs-2) bind to the same endothelial cell-specific tyrosine kinase receptor, which is activated by ang-1 but blocked by Ang-2 [27]. Angs-1 promotes endothelial cells survival, sprouting, tube formation and usually causes quiescence of endothelial cells. Angs-2 causes an activation of the endothelium [28]. Angs-2 in sera of patients with HELLP syndrome was significantly higher than those of the patients with normal pregnancy and PE [25]. In PE there was also an increase but this was not significant compared with controls [25]. Angiopoietin 1 (Angs-1) was also higher in HELLP patients compared with PE but this was not statistical significant. Compared with normal pregnant there was a significant increase of angs-1 in HELLP patients [25].

3.1.1.5. ADMA. Asymmetric dimethylarginine (ADMA) is an inhibitor of the enzyme NO synthase. ADMA reduces availability of NO which causes vasodilatation. The placenta tissue contains ADMA degrading enzyme dimethylarginine dimethylaminohydrolase (DDAH) [29]. Placental DDAH dysfunction has been suggested as one of the events involved in the development of PE and HELLP [30,31]. ADMA plasma concentrations were significantly higher in HELLP patients compared with controls. In PE patients there was no difference compared with normal pregnancies [29]. However Savvidou and al. reported a significant increase in ADMA in PE serum. In this report there was no comparison made with HELLP patients [32].

3.1.2. Growth factors

3.1.2.1. Activin and inhibin. Inhibins and activins are dimeric disulfinde-linked glycoproteins, that are members of the transforming growth factor beta (TGF-β) family of cytokines [33]. Inhibins are heterodimers consisting of one α-subunit and one of the two possible β-subunits (βA and βB subunits). There are three possible isoforms of activin, namely activin A (βA-βA), activin B (βB-βB) and activin AB (βA-βB) [34]. Recently, two additional β-subunits have been identified in mammals, named βC [35] and βE [36]. Activin A has an important influence on the survival of LSECs in synergism with VEGF. VEGF increases the production of activin A, which in turn increases the expression of VEGF receptors and amplifies the VEGF action [37,38]. Inhibin A seems to be an antagonist of activin A. This inhibition is with low affinity. When inhibin A is in combination with betaglycan it forms a stable complex and inhibits with high affinity [39]. Activin B is an important regulator of the gestation duration and onset of the parturition. Activin B deficiency lead to failed initiation of the labor altogether, resulting in sickness of the gravid mother and death of foetuses in utero. Activin B enhances Follicle stimulating hormone (FSH) release. Inhibin B causes a decrease of FSH release [40]. The feto-placental unit is the main source of circulating activin and inhibin. Secretion of activin and inhibin happens from the placental trophoblast, decidua and fetal membranes [41]. In the extravillous trophoblast cells there is an increase of inhibin A production in HELLP syndrome and also in PE. In the syncytotrophoblast cells in HELLP syndrome there is more production of activin B rather than inhibin B. In the syncytotrophoblast cells in PE there is increase of inhibin B [34]. There was no difference in expression of βC subunit and βE subunit in syncytotrophoblast and extravillous trophoblast in normal pregnancy, PE pregnancy and HELLP pregnancy [42,43].

3.1.3. Apoptosis/necrosis related factors

3.1.3.1. Fas/FasL. The Fas receptor (Fas) and Fas ligand (FasL) are part of the TNF receptor family and regulates the inflammatory response via activation and proliferation of $CD4^+$ T lymphocytes and they can activate the apoptosis pathway. FasL will bind Fas positive cells to induce apoptosis by the extrinsic pathway or activate $CD4^+$ cells [51]. Apoptosis, proliferation and FasL expression were higher in villous trophoblast in HELLP syndrome compared with control group and PE group [52]. FasL serum concentration is higher in HELLP compared with normal pregnant women [1,48,49]. Liver endothelial cells have a high expression of Fas [53]. Normally is the liver a physiological source of FasL. The placenta and the cytotoxic T lymphocytes are other sources [48,49]. Expression of FasL was not detected in the liver endothelial cells [49,53]. FasL found in the sera of HELLP women coming from the placenta, binds Fas and cause apoptotic cell death in the liver of these

patients [48]. When the LSECs are exposed to an increase of TNF-α, the expression of Fas increased, which caused a higher susceptibility to apoptosis [53].

3.1.3.2. HSPA1A/Hsp70. Serum concentrations of serum heat shock protein 70 (Hsp70/HSPA1A) levels are strongly related to the markers of haemolysis (total bilirubin level, LDH activity, plasma free haemoglobin level) as well as of hepatocellular damage (ASAT and ALAT activity). There was also a relationship between platelet count and serum Hsp70 levels [31,50]. Serum Hsp70 levels are increased and reflect inflammation, oxidative stress and hepatocellular injury. Hsp70 indicates tissue damage but may also play a role in the pathogenesis of HELLP syndrome. Extracellular Hsp70 derived from stressed and damaged necrotic cells can elicit a proinflammatory (Th1) immune response, which might be involved in the development of maternal systemic inflammatory response and resultant endothelial damage in HELLP syndrome [50]. The serum concentrations of Hsp70 are significantly higher in PE and HELLP compared with normal controls. The levels of Hsp70 are significantly higher in patients with HELLP syndrome than in preeclamptic patients [30,50].

4. Discussion

The objective of this review was to unravel which placental derived factors could have a toxic effect on the liver mimicking sinusoidal obstruction syndrome and to explore what may be the mechanisms of endothelial damage and activation of the inflammatory reaction in the liver, considering the unique liver structure of fenestrated endothelial cells within the space of Disse.

Our exploration provided possible evidence for the concept that several placental derived factors are involved in hepatic injury and cause increased apoptosis of the LSECs. The factors causing this increase of apoptosis are factors involved in the vascular homeostasis, growth factors and factors involved in apoptosis. (Table 1) These factors cause an increase of vasoconstriction by decreasing the NO production, a shift in the hemostasis by activating the platelets and an increased inflammatory state causing activation of the LSECs. This increased activation results in increased apoptosis of the LSECs, causing red blood cells able to enter the space of Disse. In the space of Disse they cause obstruction and start the formation of thrombi eventually leading to liver failure (Fig. 2).

LSECs are important fenestrated endothelial cells which allow passive molecule exchange between the hepatocytes and the sinusoids of the liver. They contribute to the regulation of sinusoidal blood flow, liver regeneration and are involved in hepatic complications. Normal fenestrae stops soluble molecules, lipoproteins, virus particles, chylomicrons and other nanoparticles with their diameter bigger than the fenestrae from entering the space of Disse. Smaller particles like chylomicron remnants can move through the fenestrae and this sieving is bidirectional. Besides that endothelial transport happens through the fenestrae it could also occur through endocytosis and transcytosis [4].

The maintenance of the LSEC and LSEC fenestration requires paracrine and autocrine cell signalling. VEGF is important in this cell signalling. VEGF stimulates NO release from NO synthase (eNOS), increased prostacyclin release and an increase of activin A [4]. Research shows that within HELLP syndrome there is an increase of VEGF but a decrease in VEGF signalling [1,9,44]. sFlt1, the soluble form of VEGFR, is increased in sera of HELLP women. This diminish the activation of VEGFR in the LSEC. Further we see in additional research an increase in sEng in the sera of HELLP women and this causes less activation of TGF receptor II (TGFRII). Less activation of this receptor diminish the release of VEGF from the LESCs, diminish the prostacyclin release and causes less vasodilatation [1,15,44]. As a compensation mechanism against the increased anti-angiogenic status the placenta increases the galectin-1 release in the serum of HELLP patients. This is a soluble pro-angiogenic factor which enhances the activation of the VEGFR by binding to neuropilin-1 (NRP-1) and causes activation of the platelets. Treatment with disaccharide lactose completely blocked the activation of the platelets [19–21]. We conclude the overall activation of the VEGFR in the LSECs is less, which causes a decrease in fenestration of the LSEC by activating the hepatic stellate cells which induces sinusoidal capillarization, less bone marrow derived progenitor cell recruitment and increased apoptosis of the LSECs. Bone marrow derived progenitor cells are involved in LSEC renewal [4,54]. Sinusoidal

Table 1
Placental factors involved in the pathogenesis of the liver in HELLP syndrome.

Factors involved in pathogenesis of HELLP syndrome						
Factors	HELLP	PE	Ref. No.	Size (kDa)	Solubility in sera	Function
Factors influencing the vasculature						
sFlt1	↑↑	↑	[1,11–15,44]	100–145	S	Anti-angiogenic; Inhibits vasodilatation; Increasing ET-1
VEGF	↑	↑↑	[1,9,44]	21–47	S	Pro-angiogenic; prevents hypertension
sEng	↑↑	↑	[1,15,44]	65	S	Inhibits TGF-β signalling; Inhibits vasodilatation; Anti-angiogenic; Influences vascular permeability
Gal-1	↑	↓	[19–21]	14.5	S	Pro-angiogenic; Matrix remodelling; Procoagulant
ET-1	↑↑	≠ *arrow*	[24,25]	24.4	/	Hypertension; Increase of hemolysis, liver enzymes, $CD4^+$ and $CD8^+$; Decrease of platelets
Angs-2	↑↑	≠ *arrow*	[25,45]	57	S	Activation of endothelium
ADMA	↑	$\uparrow^{I} 0^{II}$	[29]^{I} [32]^{II}	202	/	Inhibitor of NO synthase
Growth factors						
Inhibin A	↑	↑	[34,46]	32	S	Antagonist activin A;
Activin A	0	↑	[34,37,38,41,46]	>100	Bound to activin-binding proteins	Inhibits mitogen induced DNA synthesis; Induce apoptosis in hepatocytes; increases tubulogenesis of LSEC induced by VEGF; increases survival of LSEC
Inhibin B	0	↑	[34,40,47]	32–34	S	Decreases FSH release;
Activin B	↑	0	[34,40,46]	25.6	S	Increases FSH release; Induction of labor;
Apoptosis/necrosis related factors						
FasL/Fas	↑↑	↑	[1,48,49]	90–130	S	Induces apoptosis;
Hsp70	↑↑	↑	[30,50]	70	/	Marker of tissue damage; stimulate proinflammatory immuun response; endothelial injury

sFlt1, soluble fms-like tyrosine kinase 1, sVEGFR1; VEGF, vascular growth factor; sEng, soluble endoglin; Gal-1, Galectin-1; ET-1, endothelin-1; Angs-2, Angiotensin-2; ADMA, Asymmetric dimethylarginine;
↑,higher than pregnant controls ($p < 0.05$); ↑↑ Higher than ↑ ($p < 0.05$); ≠ *arrow* Higher than pregnant controls not significant; 0 No difference compared with controls; S soluble;/ Not described in references.

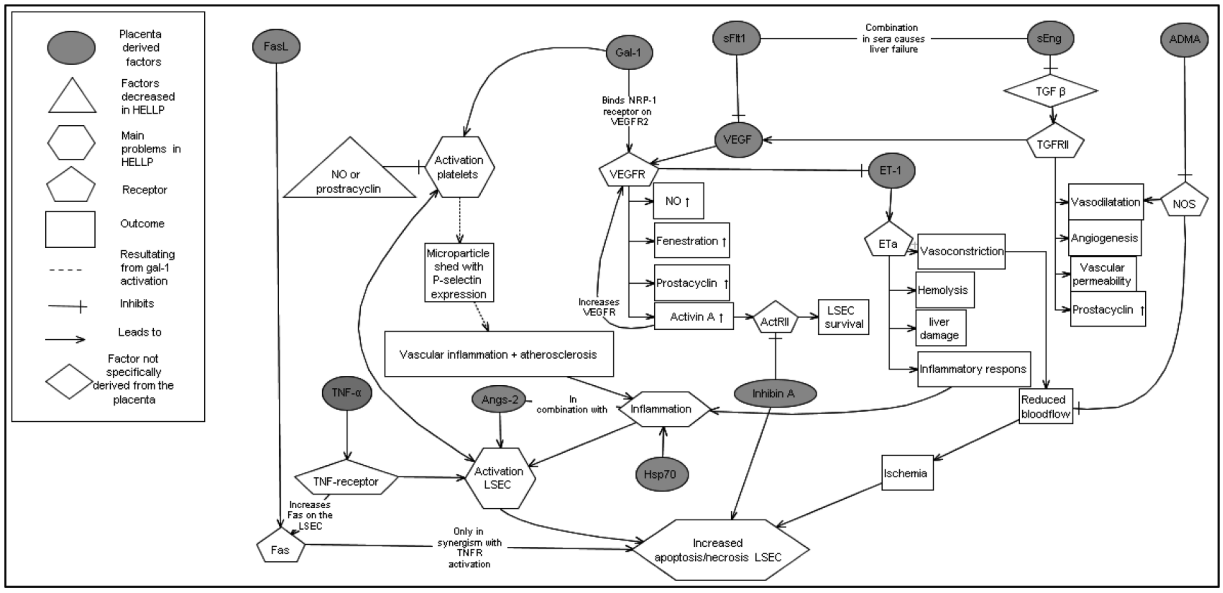

Fig. 2. Placenta derived factors involved in the pathogenesis in the liver. Gal-1: Galectin 1; NRP-1: Neuropelin-1; sFlt1: soluble fms-like tyrosine kinase 1; VEGF: Vascular Endothelial Growth Factor; VEGFR: Vascular Endothelial Growth Factor Receptor; NO: Nitric oxide; ET-1: Endothelin 1; ETa: Endothelin A receptor; sEng: soluble endoglin; TGF β: Transforming Growth Factor β; TGFRII: Transforming Growth Factor Receptor II; ADMA: Asymmetric Dimethylarginine; FasL: Fas Ligand; Hsp70: Heat Shock Protein 70; Angs-2: Angiopoietin 2; NOS: Nitric Oxide Synthase; LSEC: Liver Sinusoidal Endothelial Cells; ActRII: Activin Receptor II; TNFR: Tumor Necrosis Factor Receptor; Fas: Fas receptor.

capillarization leads to less filtration of the chylomicron remnants. This results in postprandial hypertriglyceridemia and increases the risk for atherosclerosis. It also causes an increased fibrotic state of the liver [4]. When we restore the VEGF homeostasis, the VEGFR signalling resolves the intra- and extrahepatic abnormalities that had taken place within HELLP [54].

The fenestrae from the LSECs are dynamic and the diameter is affected by sinusoidal luminal blood pressure, hormones, drugs, toxins, changes in extracellular matrix, disease, aging and exposure to environmental pollutants. Increased blood pressure causes dilatation of the fenestrae. Gal-1 causes an calcium mobilisation out of the extracellular space into the cytosol [23]. Calcium has a key role in the regulation of the fenestral diameter by activation the calcium-calmodulin-actomyosin system. An increase of intracellular calcium causes contraction of the fenestrae by this system [4,55]. When patients are treated with prostaglandin E1,intracellular calcium concentration decreases, leading to dilatation of the fenestrae [55]. A decrease in VEGFR signalling which happens in HELLP syndrome cause an increase of ET-1 [5,7,8,24,25]. Increased ET-1 causes a decrease in the diameter and a decrease in the number of the fenestrations [55].

LSECs acts as a sort of sphincter by swelling or contracting in response to vasoactive substances like ET-1, reduced NO and reduced prostacyclin thereby narrowing the sinusoidal lumen and limiting blood flow [24,25]. At these narrowing sites leukocytes might form a plug in the vessel and obstruct flow. Erythrocytes usually flow easily through such sites unless the lumen is reduced or near zero. We assume that within HELLP syndrome this narrowing is raised to its maximum because of the great increase of these vasoactive substances. This results in increased ischemia and increased coagulation.

Contact with toxins can cause LSEC swelling and gap formation by destruction of the fenestrae. The sinusoids then disintegrates and reduces blood flow. This is a mechanism seen in SOS. Galactosamine acts like a toxin and causes gap formation and swelling of the LSECs. Activin B is a factor that is increased in the sera of HELLP women. Activin B itself causes no harm to the liver because the expression of activin B in the liver is weak and activin B failed to inhibit DNA synthesis in the hepatocytes [37]. A higher expression of activin B increases FSH release. FSH contains galactosamine. It is possible that the increase in FSH could cause an increase of galactosamine exposure to the LSECs. This increased exposure to FSH which contains galactosamine could possibly result in increased necrosis of the LSEC [4,40]. NO, MMP-2 and MMP-9 inhibitor reduces LSEC injury. Inhibition of these substances exacerbated injury [4]. Inhibition of NO and MMP-9 inhibitor happens in HELLP syndrome. Gal-1 increases the expression of MMP-9 and CXCL16. NO decrease is caused by increased sFlt1, sEng, and ADMA concentration [15,29]. This results in increased injury to the LSECs and activation of an inflammation reaction by CXCL16 [19].

Activin A is a factor that contribute to the survival of the LSECs in synergism with VEGF. It is important for maintenance of the extracellular matrix from the LSECs. It stimulates collagen production in the hepatocyte stellate cells and tubulogenesis in the LSECs [38]. In HELLP patients we saw a decrease in the level of serum activin A, a decrease of the VEGF level and an increase of inhibin A. Inhibin A functions as an inhibitor of activin A. This resulted in an increased apoptosis rate of the LSECs with less restoration of them [37].

Within the sera of HELLP patients there is also an increase of FasL. FasL will bind Fas positive cells to induce apoptosis by the extrinsic pathway or activate $CD4^+$ cells [51]. The LSECs and hepatocytes have a high expression of Fas. The liver is a producer of FasL, but the expression of FasL by the liver was not detected in HELLP women. So we think the placenta is the source of the increased Fas induced apoptosis of the hepatocytes and LSECs in the liver. Cardier et al. reported that Fas ligation normally not lead to apoptosis on its own in the LSECs. LSECs are more resistant to Fas induced apoptosis pathway. Tumor necrosis factor α (TNF-α) increases the susceptibility of the LSEC by activating these cells and increasing the expression of Fas. This results in more susceptibility to Fas induced apoptosis but TNF-α does not induce apoptosis by itself [53]. The concentration of TNF- α is increased in HELLP sera [1]. So we can conclude that in HELLP syndrome there is increased activation of the LSECs by TNF- α followed by increased apoptosis by activating the Fas receptor. The FasL increased in the sera of HELLP women is a multimeric highly active form of FasL with a molecular weight between 66 and 150 kDa [48]. We assume that this form of FasL cannot pass the fenestrae of the LSECs and apoptosis of the hepatocytes happens when the LSECs degrades.

Hsp70 is a factor which is expressed by stressed and necrotic cells

and indicates tissue damage. This factor can elicit an pro-inflammatory (Th1) immune response [50]. This factor can activate endothelial cells and increase their apoptosis rate. Angs-2 is also a factor that could activate endothelial cells. Angs-2 blocks the activity of Angs-1 which exerts cell survival, sprouting, tube formation and quiescence of endothelial cells [27]. Angs-2 causes activation of endothelium in combination with an increased inflammatory state [28]. Within HELLP sera there was an increase of both Hsp70 and angs-2 so we can conclude there is more endothelial activation within HELLP syndrome, which makes the endothelial cells more susceptible to go into apoptosis [25,30,50].

5. Conclusion

With this systematic literature search, we assume that placenta derived factors could have some great influence on LSECs. Based on their function we presume they cause capillarization of the LSEC with fibrosis as a consequence, a decrease of LSEC renewal, contraction of the fenestrae, swelling of the LSECs thereby causing an obstruction in the sinusoids which limits the blood flow, increase in the activation and apoptosis of the LSECs and even some factors could cause swelling and gap formation of the LSECs. These events eventually impedes the sinusoidal flow, causes decay of the hepatocytes and eventually leads to liver failure.

This review might unravel a few hypotheses of the complicated pathophysiology of HELLP syndrome, additional research is further required.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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