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# Elevated systemic galectin-1 levels characterize HELLP syndrome

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ABSTRACT

Galectin-1 (gal-1), a member of a family of conserved β-galactoside-binding proteins, has been shown to exert a key role during gestation. Though gal-1 is expressed at higher levels in the placenta from HELLP patients, it is still poorly understood whether systemic gal-1 levels also differ in HELLP patients. In the present study, we evaluated the systemic expression of gal-1, together with the angiogenic factors, placental growth factor (PlGF) and soluble fms-like tyrosine kinase 1 (sFlt-1) in conjunction with HELLP syndrome severity. Systemic levels of gal-1 and sFlt-1 were elevated in patients with both early- and late-onset HELLP syndrome as compared to healthy controls. In contrast, peripheral PlGF levels were decreased in early- and late-onset HELLP. A positive correlation between systemic gal-1 levels and sFlt-1/PlGF ratios was found in early onset HELLP patients. Our results show that HELLP syndrome is associated with increased circulating levels of gal-1; integrating systemic gal-1 measurements into the diagnostic analyses of pregnant women may provide more effective prediction of HELLP syndrome development.


## 1. Introduction

Although HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome was described more than 30 years ago, its diagnosis remains controversial (Weinstein, 1982; O'brien and Barton, 2005). HELLP diagnosis is based on presence of hemolysis (serum lactate dehydrogenase >600 U/L, peripheral smear and indirect hyperbilirubinemia), elevated liver enzymes (serum aspartate aminotransferase >70 U/L) and low platelets ($<100 \times 10^9$/L) (Ch'ng et al., 2002; Baxter and Weinstein 2004). HELLP syndrome is thought to be a severe form of preeclampsia (PE), that can also occur in normotensive patients (Weinstein, 1982). Like PE, this syndrome is associated with both maternal and perinatal mortality, 0–15% and 20–30% respectively (Eeltink et al., 1993; Sibai and Ramadan 1993; Sibai et al., 1993; Egerman and Sibai 1999; Gasem et al., 2009). Maternal risks include liver failure, pulmonary edema, renal failure, hemorrhagic complications and death. Perinatal prognosis is poor due to preterm birth and growth restriction (Eeltink et al., 1993; Sibai and Ramadan 1993; Sibai et al., 1993; Egerman and Sibai 1999; Gasem et al., 2009). Though the pathogenesis of HELLP syndrome is not known, similar to PE, it is thought to be secondary to endothelial dysfunction and thrombotic microangiopathy. Although the role of vascular growth factors and ADAMTS 13 deficiency in HELLP syndrome has been discussed (Lattuada et al., 2003; Schutt and Minuk 2007), the pathophysiological basis of HELLP syndrome remains uncertain, which compromises the development of preventive medicine.

Galectin-1 (gal-1) is a β-galactoside-binding lectin (Barondes et al., 1994) that influences key processes associated with a healthy gestation such as decidualization, maternal immune adaption, trophoblast cell differentiation and angiogenesis (Barrientos et al., 2014). Regulated by ovarian hormones (estrogens and progesterone) (Von Wolff et al., 2005), gal-1 is spatiotemporally expressed in many different cell types during pregnancy, including fetal trophoblast and decidual immune cells. In the context of human trophoblast differentiation, gal-1 is involved in two processes: (a) promotion of syncytium formation (Fischer et al., 2010; Tirado-Gonzalez et al., 2013; Hutter et al., 2015) and (b) extravillous trophoblasts (ETV) invasiveness (Kolundzic et al., 2011, 2015; Tirado-Gonzalez et al., 2013). These processes contribute to pla-

*Abbreviations:* HELLP, hemolysis elevated liver enzymes and low platelets; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase; gal-1, galectin-1; PE, preeclampsis; ETV, extravillous trophoblasts; uNK, uterine natural killer cells.

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**Table 1**
Characteristics of the recruited participants included in this study with gestation age <34 weeks (early onset HELLP).

| Parameters | Normal ($n = 45$) | Early onset HELLP ($n = 7$) |
|---|---|---|
| Age (years) | 33.2 ± 5.7 | 32.7 ± 4.0 |
| GA | 13–34 | 26–33 |
| BMI (kg/m2) | 23.9 ± 4.6 | 28.5 ± 5.7 |
| GA at birth | 39.7 ± 2.5 | 29.7 ± 2.9 |
| Birth Weight (Percentile) | 52.8 ± 27.9 | 8.6 ± 7.6** |
| Platelets (/μl) | 187,800 ± 60,000 | 109,857 ± 51,673** |
| AST (U/L) | 70.1 ± 155.3 | 269.0 ± 268.2** |
| ALT (U/L) | 12.3 ± 4.3 | 306.3 ± 213.7** |
| Proteinuria (mg/mmol) | 0.54 ± 0.85 | 4.24 ± 5.03 |
| SBP (mm Hg) | 117.5 ± 14.6 | 153.6 ± 12.7 |
| DBP (mm Hg) | 74.3 ± 10.7 | 93.1 ± 14.3 |

*Abbreviations*: GA: gestational age in weeks; BMI: Body Mass Index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; SBP: systolic blood pressure; DBP: diastolic blood pressure. *Note*: Exclusion criteria: pregnant women with underlying conditions such as obesity, diabetes mellitus type I or type II, cardiovascular diseases including high blood pressure, autoimmune diseases, hormonal disorders, previous history of recurrent abortions or infertility, chronic diseases, any permanent medication or a smoking habit, pathological pregnancy progression such as an isolated intrauterine growth retardation, preeclampsia, intrauterine infections, premature labor (not in relation to HELLP-Syndrome), placenta praevia, bleedings and other placental or foetal abnormalities, multiples.

** denotes $P < 0.01$ as analysed by the Mann–Whitney $U$ Test.

**Table 2**
Characteristics of the recruited participants included in this study with gestation age >34 weeks (late onset HELLP).

| Parameters | Normal ($n = 41$) | Late onset HELLP ($n = 14$) |
|---|---|---|
| Age (years) | 32.1 ± 4.7 | 34.3 ± 4.6 |
| GA | 34–42 | 34–41 |
| BMI (kg/m$^2$) | 27.1 ± 7.6 | 26.5 ± 5.9 |
| GA at birth | 39.9 ± 1.6 | 36.5 ± 2.4 |
| Birth weight (Percentile) | 42.6 ± 22.9 | 15.5 ± 15.1** |
| Platelets (/μl) | 206,310 ± 63,334 | 130,142 ± 65,084 |
| AST (U/L) | 66.9 ± 164.1 | 176.2 ± 308.9** |
| ALT (U/L) | 80.5 ± 239.3 | 140.0 ± 200.7** |
| Proteinuria (mg/mmol) | 0.17 ± 0.07 | 4.23 ± 5.18** |
| SBP (mm Hg) | 123.9 ± 14.3 | 147.4 ± 14.5 |
| DBP (mm Hg) | 79.1 ± 12.7 | 91.3 ± 12.0 |

*Abbreviations*: GA: gestational age in weeks; BMI: Body Mass Index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; SBP: systolic blood pressure; DBP: diastolic blood pressure. *Note*: Exclusion criteria: pregnant women with underlying conditions such as obesity, diabetes mellitus type I or type II, cardiovascular diseases including high blood pressure, autoimmune diseases, hormonal disorders, previous history of recurrent abortions or infertility, chronic diseases, any permanent medication or a smoking habit, pathological pregnancy progression such as an isolated intrauterine growth retardation, preeclampsia, intrauterine infections, premature labour (not in relation to HELLP-Syndrome), placenta praevia, bleedings and other placental or foetal abnormalities, multiples.

** denotes $P < 0.01$ as analysed by the Mann–Whitney $U$ Test.

cental function by promoting maternal immune adaptation during early gestation. At the maternal site, a unique uterine natural killer (uNK) cell subset that selectively expresses gal-1 characterizes a healthy decidua. This uNK derived gal-1 promotes apoptosis of decidual activated T cells, thus, preventing damage to the developing embryo (Koopman et al., 2003; Kopcow et al., 2008, 2010). Just as gal-1 is an important player in healthy pregnancy, dysregulated gal-1 expression is also described in pregnancy pathogenesis. We recently described that inhibition of gal-1-mediated angiogenesis resulted in a PE-like syndrome in mice (Freitag et al., 2013). Furthermore, placental gal-1 expression was down-regulated in patients diagnosed with early onset PE, which is mainly a consequence of placental dysfunction (Freitag et al., 2013). In connection with HELLP, gal-1 was found to be significantly up-regulated in villous trophoblast tissue of HELLP placentas (Jeschke et al., 2007). This knowledge invites further exploration of the potential link between gal-1 and angiogenic factors (*e.g.*, placental growth factor (PlGF) and soluble fms-like tyrosine kinase 1 (sFlt-1)) in the pathophysiology of HELLP syndrome.

The aim of this study was to investigate how systemic gal-1 and other angiogenic factors fluctuate during the course of HELLP syndrome. We determined serum concentrations of gal-1, PlGF and sFlt-1 in both healthy and HELLP diagnosed pregnant women and examined these factors in association with disease severity.

## 2. Materials and methods

### 2.1. Study patients

For analyses of gal-1, sFlt-1 and PlGF levels during normal and HELLP pregnancy, blood samples were collected from healthy pregnant women ($n = 86$) and pregnant women diagnosed with HELLP syndrome ($n = 21$) in the second and third trimester of pregnancy at their planned visits at the Klinik St. Hedwig, Barmherzige Brüder, Klinik für Geburtshilfe und Frauenheilkunde der Universität Regensburg, Germany. All patients involved in this study were properly informed about the purpose of our research and gave their written consent before the sampling. The study was approved by the ethics committee of the University of Regensburg (23.02.2012). Characteristics of the recruited participants are summarized in Table 1. Diagnosis of HELLP was based on the criteria proposed by the German guidelines of hypertensive disorders during pregnancy http://www.awmf.org/uploads/tx_szleitlinien/015-018l_S1_Diagnostik_Therapie_hypertensiver_Schwangerschaftserkrankungen. The control population consisted of 86 healthy pregnant women without any maternal or fetal disorders. Groups were matched by ethnicity (self-referred). Controls and patients were not matched with regard to age, parity or gestational age, as all criteria in our study population were very similar (Tables 1 and 2). Parity never exceeded two. Patients were classified by the gestational age blood taken (>/<34 weeks of pregnancy).

Inclusion criteria for both groups were: singleton pregnancy with living fetus, and gestational age between 20 to 42 weeks. Exclusion criteria for both groups were: autoimmune diseases, pre-existing diabetes, uterine malformation, pregnancy resulting from *in vitro* fertilization, placental abruption, infection, cancer or any other systemic disease, including pre-existing hypertension. We also excluded women with solid organ transplantation and the use of steroids, antibiotics, immunosuppressants, antihistamines or anti-inflammatory medication.

### 2.2. Data collection

Patient's characteristics and medical history were collected by routine assessment in our clinic by a medical nurse and physician. Detailed information concerning the pregnancy and conception status was also obtained through pregnancy records (Mutterpass). Blood pressure, blood and urine samples were taken at first contact and followed as needed by clinical routine and medical course. Patients and controls were examined before labor started (including ultrasound), when they had minor contractions, immature cervical examination, no membrane breakage and no vaginal bleeding. Blood was taken after the examination. Routine measurements (such as thrombocytes, hemoglobin, coagulation parameters, liver enzymes, *e.g.*) were performed by the Department of Clinical Chemistry (Klinik St. Hedwig, Barmherzige Brüder, Klinik für Geburtshilfe und Frauenheilkunde der Universität Regensburg, Germany) and documented using the SAP computer system. Treatment decisions were made according to the German guidelines for hypertensive disorders during pregnancy.

### 2.3. Determination of gal-1 by ELISA

Human gal-1 levels were measured with a specific sandwich ELISA protocol, as reported previously (Tirado-Gonzalez et al., 2013). Briefly, immunolon 2 ELISA plates (Dynatech Laboratories, USA) were covered with polyclonal anti human gal-1 antibody (2 μg/ml; R&D Systems, USA), and washed with washing buffer (0.5% Tween-20 in PBS). Plates were blocked with 1% BSA in PBS. Individual wells were incubated with serial dilutions of gal-1 or serum samples (diluted 1/20) for 1 h at room temperature. Wells were washed and incubated with biotinylated polyclonal anti-human gal-1 antibody (0.25 μg/ml in PBS 0.1% BSA; R&D Systems, USA). Plates were washed 6 times and incubated with horseradish peroxidase (HRP)-conjugated streptavidin (Calbiochem, USA). After 8 additional washes, a colorimetric reaction was developed with 3,3,5,5′-tetramethyl benzidine (TMB) substrate (Pierce Biotechnology, USA). The reaction was stopped by adding one volume of 4 N $H_2SO_4$. Absorbance at 450 nm was recorded.

### 2.4. Determination of sFlt-1 and PlGF

After drawing venous blood from patients with a 7.5 ml S-Monovette® (Sarstedt, Nümbrecht, Germany), the samples were centrifuged at 2000 × *g* for 10 min at room temperature. Afterwards serum was transferred to cryotubes (Thermo scientific, Roskilde, Denmark) and frozen at −20 °C. Concentrations of soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) were determined by Elecys electrochemiluminescience sandwich ELISA. The analysis was performed by a Cobas e 411 analytical device (Roche, Mannheim, Germany). Briefly, samples were incubated with the sFlt-1- respectively PlGF- specific biotinylated monoclonal antibodies and a ruthenium-complex marked monoclonal sFlt-1-/PlGF- antibodies to form complexes. Those complexes were fixed at a solid phase (by adding streptavidin-covered microparticles). Chemiluminescence-emission was induced by adding voltage and is measured by a photomultiplier. (Roche, Mannheim, Germany).

### 2.5. Statistics

Data are expressed as mean ± SD. Non-parametric Mann–Whitney *U*-test were applied. All *p*-values are two-tailed and $p < 0.05$ was considered significant.

## 3. Results

### 3.1. Clinical characteristics of patient's cohort

Total of 107 individuals were included in the study, of which 21 patients had HELLP syndrome. Patients with HELLP were divided in two categories according to early- (<34 weeks, also known as severe HELLP) and late- (>34 weeks) onset HELLP. As shown in Table 1, the average age of participants with normal gestation at delivery was 33.2 years (standard deviation = 5.7 years) and patients who developed early onset HELLP syndrome was 32.7 years (standard deviation = 4.0 years). No differences were found between both normal and early onset HELLP patients with respect to the gestation age, body mass index and gestation age at birth. As expected, early onset HELLP patients had significantly more elevated liver enzymes (such as AST and ALT) and a lower platelet count compared to controls (Table 1). In addition, newborn birth weight was also decreased in early onset HELLP patients when compared with controls. No other biochemical parameters (such as proteinuria, systolic blood pressure; SBP and diastolic blood pressure; DBP) were significantly associated with early onset HELLP patients (Table 1). In our late onset HELLP patients we observed increased urinary protein concentrations and elevated liver enzymes (AST and ALT) and a lower birth weight compared to controls (Table 2). No differences were found in systolic and diastolic blood pressures between both patient groups. In this cohort, few women developed proteinuria and elevated blood pressure after being diagnosed with HELLP. No women were prediagnosed with PE (Tables 1 and 2). The majority of the patients included within the control group had a spontaneous vaginal delivery, whereas C-section was the predominant mode of delivery in the early and later onset HELLP patients (Table 3).

**Table 3**
Mode of Birth for patients included in this study.

| Parameters | Normal ($n = 86$) | Early and late onset HELLP ($n = 21$) |
|---|---|---|
| Mode of birth | | |
| Spontaneous birth | 52 (60.5%) | 3 (14.3%) |
| Caesarean section | 31 (36.0%) | 18 (85.7%) |
| Vaginal-operative birth | 3 (3.5%) | – |

*Note*: Numbers in total and percentage; Caesarean includes both primarily or secondary.

**Table 4**
Correlation analysis of serum gal-1 and platelet accounts.

| Patients | Spearman correlation coefficient | *p* value |
|---|---|---|
| Normal ($n = 45$) | −0.2167 | NS |
| Early onset HELLP ($n = 7$) | −0.5118 | <0.05* |
| Normal ($n = 41$) | 0.0773 | NS |
| Early onset HELLP ($n = 14$) | −0.1492 | NS |

NS: not significant.
* denotes ($p < 0.05$).

### 3.2. The anti-angiogenic milieu in early and late onset HELLP syndrome was accompanied by increased systemic gal-1

Next, we measured anti-angiogenic markers and gal-1 levels in our patients and controls. Fig. 1 summarizes the levels of angiogenic markers in relation to the pregnancy outcome. Levels of PlGF (Fig. 1A) decreased whilst sFlt-1 (Fig. 1B), and sFlt-1/PLGF ratio (Fig. 1C) significantly increased in women with early-onset HELLP syndrome (before 34 weeks of gestation). In addition, gal-1 systemic levels (Fig. 1D) were increased in patients with early-onset HELLP compared with controls. Fig. 1E shows a Spearman rho correlation of sFlt-1/PLGF ratio with gal-1 in normal gestation and early- onset HELLP syndrome. There was no significant correlation between the sFlt-1/PLGF ratio and gal-1 systemic levels in controls and early onset HELLP patients (Fig. 1E, $p > 0.05$). However, in patients with early onset HELLP syndrome, gal-1 was found to correlate positively with the sFlt-1/PLGF ratio (Fig. 1E, bottom panel). In addition to this finding, there was a significant negative correlation between the systemic gal-1 levels and platelet account in early onset HELLP syndrome patients (Table 4).

The angiogenic factors were also analysed in patients with late onset HELLP syndrome. Fig. 2 shows that women who developed late onset HELLP had lower levels of PlGF (Fig. 2A), increased sFlt-1 (Fig. 2B) and increased ratio of sFlt-1/PlGF (Fig. 2C) compared with controls. In addition, gal-1 systemic levels (Fig. 2D) were higher in women who developed late onset HELLP syndrome compared to patients with normal pregnancy. However, there was no significant correlation between sFlt-1/PLGF ratio or platelet account (Table 4) and gal-1 systemic levels in controls and late onset HELLP patients (Fig. 2E).

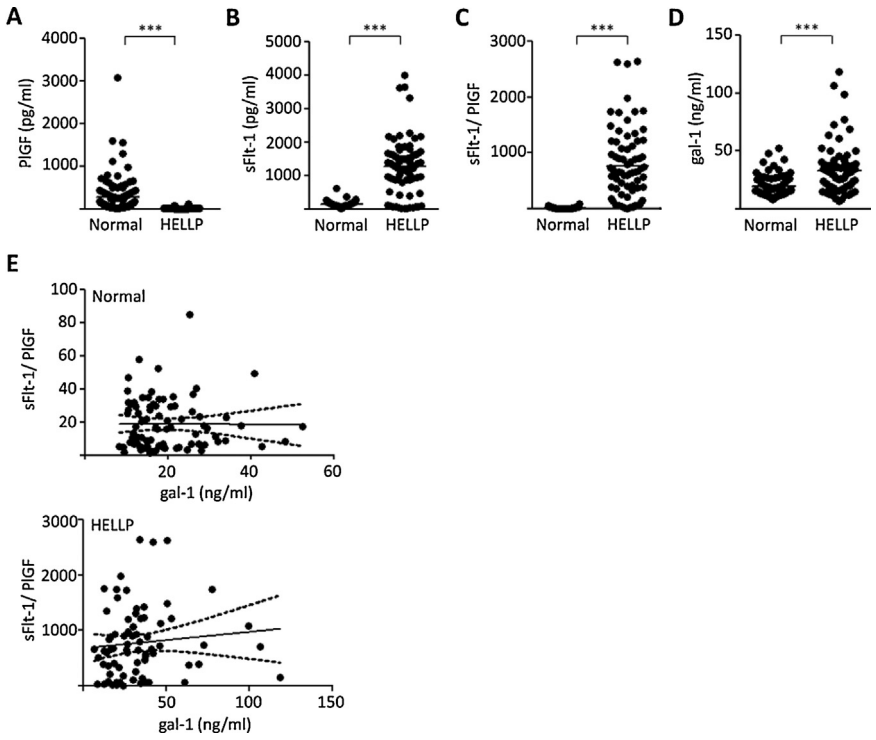


**Fig. 1.** Serum levels of PlGF, sFlt-1 and gal-1 among normal and early onset HELLP patients. (A,B) Comparision of plasma placental growth factor (PlGF;A) and soluble fms-like tyrosin kinase 1 (sFlt-1;B) in normal pregnant women ($n = 86$) with early onset HELLP women ($n = 7$). (C) sFlt-1:PlGF ratio compared with women who developed early onset HELLP or normal pregnancy. (D) Systematic gal-1 levels as measured by ELISA. Gal-1 serum levels from patients with early onset HELLP pregnancy were increased compared to control normal pregnant patients. (E) Scatterplots showing distribution of individual values of soluble fms-like tyrosine kinase 1/placental growth factor (sFlt-1/PlGF) ratio and gal-1 in cases of normal (top panel) and early onset HELLP (bottom panel) patients, obtained from maternal serum before 34 weeks of gestation. (Top panel) $r^2 = -0.0091$; (Bottom panel) $r^2 = 0.1005$. Dotted curves show 95% confidence band of the best-fit line. Results are presented as mean (*** denotes $p < 0.001$ as analysed by the Mann–Whitney $U$ test).

## 4. Discussion

HELLP syndrome causes detrimental maternal and perinatal prognoses in patients, resulting in substantial costs for health services. The pathophysiology of the HELLP syndrome is currently unknown and, to date, delivery remains as one of the only methods of disease management. Therefore, early diagnosis of this disease will have maternal and perinatal benefits, and contribute to a substantial reduction in health services costs. Though there are currently no HELLP syndrome biomarkers, we were able to show a significantly increased level of systemic gal-1 during the course of HELLP, regardless of disease severity. These results suggest that the kinetics of gal-1 during HELLP is different from PE patients. In this context, we recently showed that only patients with late onset PE had increased gal-1 systemic levels, while no changes were observed during the course of early onset PE (Freitag et al., 2013). Of note, we analyzed only non-laboring patients without membrane breakage and no uterine contractions that were mainly admitted for c-section delivery in both pregnancy cohorts. All patients were physically examined before blood samples were taken. Even if contractions were reported, none of these women showed cervical dilation. This implies a minimum effect of parturition on oxidative stress in our early onset HELLP patients, suggesting that the differences in gal-1 levels observed are not a consequence of the inflammatory pathway associated with preterm labor (Velez et al., 2008). The increase in circulating gal-1 levels during the course of early onset HELLP syndrome suggests that HELLP may be incorrectly characterized as being a severe form of PE. Therefore, it is attractive to hypothesize that HELLP syndrome may share some features with PE, but constitute a separate pregnancy complication entity.

Since gal-1 promotes angiogenesis during gestation, our results also suggest that increased peripheral levels of gal-1 in HELLP patients represent an adaptation mechanism to compensate for the severe anti-angiogenic status in these patients. Increased peripheral levels of gal-1 in HELLP patients are attributed in part to the placental gal-1 overexpression (Jeschke et al., 2007). The variety of pro-angiogenic effects currently ascribed for gal-1, particularly its interactions with the VEGF signaling pathway, acts in support of this notion (Blois et al., 2015). During pregnancy, angiogenic responses associated with implantation, decidualization and placental development are triggered by binding of VEGF to VEGFR2 on endothelial cells (Halder et al., 2000; Douglas et al., 2009). Gal-1 has been found to further enhance endothelial cell migration and adhesion by stabilizing this interaction through binding the VEGF co-receptor NRP-1 (Hsieh et al., 2008; Douglas et al., 2009; Freitag et al., 2013). In this context, it is feasible that the potent anti-angiogenic milieu typical of HELLP (*i.e.*, decreased cytotrophoblast VEGF expression, increased sFlt-1 secretion in the maternal circulation and reduced placental p38α MAPK signaling; (Zhou et al., 2002; Corradetti et al., 2010) leads to systemic and local up-regulation of gal-1 as a compensatory response to cope with defective angiogenesis.

On the other hand, recent research on the role of gal-1 in platelet biology suggests that dysregulation of this lectin could also underlie the thrombocytopenic status and thus directly influence the triad signs of HELLP syndrome (Haram et al., 2009). Decreased platelet count, is mandatory for HELLP diagnosis. Platelet activation, and subsequent adhesion to damaged vascular endothelial cells and aggregation, results in increased platelet turnover with a shorter lifespan (Redman et al., 1978; Stubbs et al., 1986). In this regard, gal-1 has been shown to trigger diverse platelet activation responses

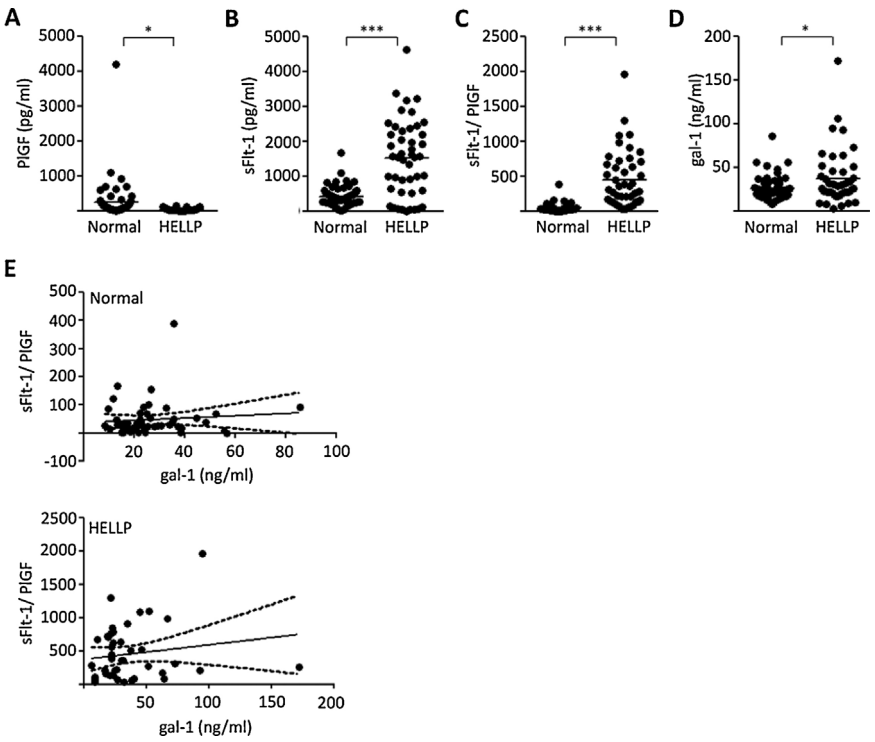


**Fig. 2.** Serum levels of PlGF, sFlt-1 and gal-1 among normal and late onset HELLP patients. (A,B) Comparision of plasma placental growth factor (PlGF;A) and soluble fms-like tyrosin kinase 1(sFlt-1;B) in normal pregnant women and patients with late onset HELLP. (C) sFlt-1:PlGF ratio compared normal patients with women who developed late onset HELLP. (D) Systematic gal-1 levels as measured by ELISA. Gal-1 serum levels from patients with late onset HELLP pregnancy were increased compared to control normal pregnant patients. (E) Scatterplots showing distribution of individual values of soluble fms-like tyrosine kinase 1/placental growth factor (sFlt-1/PlGF) ratio and gal-1 in cases of normal (top panel) and late onset HELLP (bottom panel) patients, obtained from maternal serum after 34 weeks of gestation. (Top panel) $r^2 = 0.09225$; (Bottom panel) $r^2 = 0.09719$. Dotted curves show 95% confidence band of the best-fit line. Results are presented as mean(* and *** denote $p < 0.05$ and $p < 0.001$ respectively as analysed by the Mann–Whitney *U* test).

including F-actin polymerization, increased P-selectin expression, exposure of fibrinogen binding sites and promotion of homotypic and heterotypic aggregation; induced upon binding of the lectin to the αIIbβ3 integrin receptor (Pacienza et al., 2008; Romaniuk et al., 2012). Moreover, human platelets themselves are a source of gal-1 expression, which was shown to contribute to agonist-induced activation responses (Pacienza et al., 2008). Interestingly, these authors observed that direct platelet aggregation was dependent on relatively high gal-1 concentrations, similar to those that may occur at sites of tumor growth and inflammation. It is thus possible that in the context of HELLP, increased concentrations of gal-1 released to the maternal circulation may directly influence platelet activation responses and contribute to the overt clinical manifestation of the syndrome. Indeed, our results showed that patients with early onset HELLP have a significant negative correlation between systemic gal-1 levels and platelet count.

Finally, our study highlights a potential physiopathological link between elevated systemic concentrations of gal-1 and HELLP syndrome. Several studies have already discussed the uses and limitations of sFlt-1/PlGF ratio measurement in complicated pregnancies, highlighting the notion ratios prove particularly useful in patients with the most severe disease progression (*i.e.*, early onset PE and HELLP) (Schaarschmidt et al., 2013; Herraiz et al., 2014; Andersen et al., 2015). By showing a positive correlation between systemic gal-1 levels and sFlt-1/PlGF ratios in early onset HELLP patients, our results invite further exploration of the potential combined use of both markers to improve diagnosis and discrimination between clinical entities. Whether dysregulation of gal-1 in the context of HELLP is consequence of the poor angiogenic status or a causative for the overt clinical manifestations requires further investigation. Dissecting the implications of gal-1 mediated pathways during pregnancy will certainly contribute to a better understanding of these complex diseases and improve our chances for successful diagnosis and intervention.

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