Soluble fms-like tyrosine kinase 1 (sFlt-1) - a novel biochemical marker for acute fatty liver of pregnancy: a prospective observational study

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Abstract

Objective Acute fatty liver of pregnancy (AFLP) substantially contributes to maternal and neonatal morbidity and mortality. The aim of this study was to investigate angiogenic profiles by measuring soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PLGF) in pregnancies compromised by AFLP and to compare them to those complicated by HELLP (haemolysis, elevated liver enzyme, low platelet) syndrome. Methods In pregnant patients affected by AFLP or HELLP syndrome sFlt-1 and PLGF serum levels were measured. To assess the diagnostic potential of these angiogenic markers in AFLP as well as discriminating it from HELLP syndrome, non-parametric tests were used and receiver-operating-curves (ROC) were calculated. Results Six cases with AFLP and 48 women with HELLP syndrome were included into the study. Patients with AFLP showed significantly higher sFlt-1 levels (median: 57570pg/ml [range: 31609-147170pg/ml]) than patients with HELLP syndrome (9713pg/ml [1348-30781pg/ml ; p<0.001). PLGF serum levels were increased in patients with AFLP compared to those with HELLP syndrome (197 pg/ml [127-487pg/ml] versus 40 pg/ml [9-644pg/ml], respectively, p<0.01,). sFlt-1/PLGF-ratios were not significantly different between AFLP and HELLP syndrome patients (192 [157-1159] versus 232 [3-948], respectively, NS). A sFlt-1 cut-off value of 31100pg/ml allowed differentiating between these two diseases with a sensitivity and specificity of 100%. Conclusions AFLP is associated with very high serum levels of sFlt-1. Besides the suggested Swansea criteria to diagnose AFLP a sFlt-1 value above 31100 pg/ml may be also an additional biochemical feature improving discrimination between AFLP and HELLP syndrome. Funding:NA Keywords:AFLP, HELLP syndrome, preeclampsia, sFLT-1, PLGF

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Short title: Acute Fatty Liver of Pregnancy and angiogenic markers

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Methods

In pregnant patients affected by AFLP or HELLP syndrome sFlt-1 and PLGF serum levels were measured. To assess the diagnostic potential of these angiogenic markers in AFLP as well as discriminating it from HELLP syndrome, non-parametric tests were used and receiver-operating-curves (ROC) were calculated.

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Funding: NA

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Tweetable abstract:

Soluble fms-like tyrosine kinase 1 (sFlt-1) may serve as a novel biochemical marker for acute fatty liver of pregnancy

Introduction

Hypertensive pregnancy diseases affect up to 10 % of all pregnancies worldwide.[1,2] Among them are preeclampsia, characterized by hypertension and proteinuria as well as HELLP syndrome, a multisystemic disorder, defined by haemolysis, elevated liver enzymes and low platelet count.[3] The HELLP syndrome shares a variety of features with other liver diseases, which compromise approximately 3% of all pregnancies worldwide.[4] Acute fatty liver of pregnancy (AFLP) is a rare but often devastating disease with an incidence that varies between 1:7000 and 1:20'000 pregnancies.[5] AFLP and HELLP syndrome share multiple clinical symptoms and up to date for both clinical conditions delivery remains the only treatment. Some clinical approaches recommend immediate delivery in AFLP whereas in HELLP syndrome delivery can be delayed, in particularly before 34 gestational weeks to assure fetal lung maturation following corticoid administration. [6-8] Compared to HELLP syndrome AFLP, however, carries an even higher risk of adverse maternal and fetal outcome.[9] Patients affected by HELLP syndrome with or without preeclampsia and those compromised by AFLP share - apart from clinical features - also common laboratory findings such as thrombocytopenia, haemolysis and especially elevated liver enzymes.[10] A prerequisite for prompt diagnosis is a robust diagnostic tool to differentiate between these liver-associated pregnancy complications with clinical and laboratory overlapping features.

The gold standard for the diagnosis of AFLP is histological confirmation following liver biopsy. These interventions, however, are rarely performed due to the risk of haemorrhages and the urgent need to deliver affected patients. Therefore, non-invasive Swansea criteria have been proposed to identify patients with AFLP.[5, 11] In a large population-based prospective study, Knight et al have shown that six or more Swansea criteria reasonably well agreed with the clinical diagnosis.

Angiogenic factors play an important role in the pathogenesis of placenta-associated complications such as preeclampsia with and without HELLP syndrome.[12] Angiogenic profiling using sFlt-1/PLGF ratio can be helpful to identify women with impending preeclampsia and these markers have also the potential to tailor the management in women with established preesclampsia although this point is still controversial.[13-15] The data on angiogenic factors in AFLP is scarce. Initial studies investigating the angiogenic status in AFLP patients assume that the anti-angiogenic condition aggravates compared to patients with HELLP syndrome.[16, 17]

The aim of this study was to analyse the angiogenic profile in pregnancies compromised by AFLP and to assess whether angiogenic factors may be useful to discriminate between AFLP and HELLP syndrome.

Methods

Pregnant women with HELLP syndrome with or without preeclampsia as well as features of AFLP at our referral institution between 2011 and 2018 were prospectively enrolled. At admission serum levels of sFlt-1 and PLGF were measured using electro-chemiluminescence immunoassays (ELECSYS; Roche Diagnostics GmbH, Mannheim, Germany) on Cobas e 601 analyzer (Hitachi High Technology Co, Tokyo, Japan). Dilutional series were performed using human serum in a ratio of 1:10 in patients with sFlt-1 values beyond the detection limit of 85.0 ng/ml. Clinical and obstetrical data were retrieved from patient charts.

HELLP syndrome was defined according to Tennessee and Mississippi classification as lactate dehydrogenase (LDH) [?]600U/l as a surrogate marker of haemolysis, alanine and aspartate transaminase (ALT/AST) [?]70U/l for elevated liver enzymes. We included only patients having platelets count of less than 100G/l according to the statment of ISSHP and the guideline of the German Society of Gynecology and Obstetrics[18, 19]. Hence, class 3 of the Mississippi classification (platelet 100 to 150 G/L) was not taken into account, as it is considered more as a transient form of HELLP syndrome.[18]

Preeclampsia was defined, according to the revised statement of the international society for the study of hypertension in pregnancy (ISSHP) 2014, as chronic or gestational hypertension (blood pressure [?]140/90mmHg in at least two measurements) accompanied by significant proteinuria ([?]300mg/24h) or signs of utero-placental dysfunction with fetal growth restriction (FGR) or maternal endothelial dysfunction.[3] According to this ISSHP statement, patients were considered suffering from a severe preeclampsia when showing severe hypertension ([?]160/110mmHg), signs of impending eclampsia (headache, visual disturbances) or when diagnosed with HELLP syndrome.

Fetal growth restriction (FGR) was defined as fetal abdominal circumference <5th percentile or estimated fetal weight <10th percentile for gestational age with altered fetal and/or maternal hemodynamic or an abnormal growth trajectory over time.[20, 21]

We used the Swansea criteria as a diagnostic tool for AFLP. Patients were considered being positive if at least 6 criteria were present.[5] To correct for gestational age-dependent angiogenic profile pattern, the time points of blood draw were matched (+- 1 week) and each AFLP case was matched with two patients with HELLP syndrome with and without preeclampsia.

Statistical analysis was performed with GraphPad Prism version 8.0 for Windows (GraphPad Software, San Diego, CA, USA). Continuous variables were analysed using parametric and nonparametric tests. Proportions were analysed using Chi^2-test or Fischer's exact test where appropriate. Correlations between numerical parameters were analysed using the Spearman's rho bivariate correlation test. A receiver operating characteristic (ROC) curve analysis was used to describe the relationship between sensitivity and false-positive rate for different angiogenic values to predict AFLP. A p-value of <0.05 was considered for significancy. The study was approved by the institutional ethics committee of the canton of Bern (Kantonale Ethikkommission Bern, Ref.-Nr.: 365/15).

Results

In this study 54 patients were prospectively enrolled. 48 women were diagnosed with HELLP syndrome while six women fulfilled six or more Swansea criteria and therefore were diagnosed with AFLP. The clinical characteristics of the study population are depicted in Table 1.

AFLP patients showed impressively high sFlt-1 levels up to 147170pg/ml (median: 57570pg/ml [range: 31609-147170pg/ml]) which were significantly higher than those found in patients with HELLP syndrome (9713pg/ml [1348-30781]pg/ml; p<0.001; Figure 1).

PLGF serum levels were higher in patients with AFLP than in those with HELLP syndrome (median: 197 pg/ml [range 127-487pg/ml] versus 40 pg/ml [9-644pg/ml], p<0.01; Figure 2).

sFlt-1/PLGF-ratios were not significantly different between AFLP and HELLP syndrome patients (192 [157-1159] versus 232 [3-948]; NS); (Figure 3).

ROC analysis was performed to assess the test performance of sFlt-1 and PLGF in discriminating between AFLP and HELLP syndrome. A sFlt-1 cut-off value of 31.2 ng/ml allowed differentiating between these two diseases with a sensitivity and specificity of 100%. For PLGF on the other hand the area under the ROC curve was 0.89 (95%CI 0.79-0.98; p<0.005). A PLGF cut-off value of 110 g/ml showed a sensitivity of 100% with a specificity of 81 % in distinguishing between AFLP and HELLP syndrome.

To correct for a potential gestational age-dependent bias regarding the angiogenic parameters patients with AFLP and HELLP syndrome were matched (+-1 week) on a 1:2 basis. Compared to gestational age-matched HELLP syndrome patients median [range] sFlt-1 serum levels were still higher in AFLP patients (HELLP: 9209 pg/ml [2544-30781] versus AFLP: 57570 pg/ml [range: 31609-147170pg/ml]; p<0.001). Similarly, median PLGF serum concentrations were higher in AFLP patients when compared to women affected by HELLP syndrome; (AFLP: 197pg/ml [127-487pg/ml; n=6] versus HELLP: 57pg/ml [17-232 pg/ml; n=12], p<0.01). Since serum levels of both sFlt-1 and PLGF were elevated in patients with AFLP when compared with those affected by HELLP syndrome sFlt-1/PLGF-ratio were not significantly different between AFLP and HELLP syndrome patients (AFLP: 192 [157-1159] versus HELLP: 202 [17-832], respectively, p=NS). There was no overlap in sFlt-1 serum concentrations between theses matched groups, a sFlt-1 cut-off value of 31100 pg/ml differentiated perfectly between the two pregnancy complications.

Three out of six patients (50%) in the AFLP group showed sFlt-1 levels over the threshold of the test detection limit of 85.0 ng/ml. Performing dilution series with human serum 1:10, sFlt-1 levels up to 147170 pg/ml were detected.

Further analysis showed that no FGR was found in the off-springs of our AFLP cohort, whereas 48% of all off-springs following pregnancies affected by HELLP syndrome were considered as FGR. (Table 1)The rate of NICU admission was comparable between neonates following pregnancies with AFLP and HELLP syndrome, however AFLP off-springs showed significantly lower umbilical cord artery pH values than their peers following HELLP syndrome: AFLP: 7.23 (7.11-7.28 versus HELLP: 7.33 (7.12-7.38; $p<0.01$). Apgar scores as well as maternal age or BMI did not differ significantly between the two groups although 50% of the neonates in the AFLP group had an Apgar score at 5 minutes of <7.0 No significant difference was found in aminotransferases concentrations between women affected by HELLP syndrome and AFLP.

Discussion

Main Findings and Interpretation:

Our data demonstrate that pregnancies compromised by AFLP show exceedingly higher sFlt-1 and higher PLGF serum levels compared to pregnancies affected by HELLP syndrome. This biochemical phenomenon should focus our attention to diagnose or to rule out AFLP in women presenting with pregnancy-associated liver disorders. Moreover, this altered angiogenic pattern also underscores that AFLP and HELLP syndrome are two distinct entities. Similar to our findings, compared to pregnancies comprised to HELLP syndrome, altered angiogenic profile patterns were found in AFLP patients in a case reports as well as in case series.[16, 17] These reports together with our findings are important novel insights, particularly since prospective studies will barely succeed due to the extremely low incidence of AFPL.[5]

Clinically it may be difficult to distinguish AFLP from other pregnancy-related diseases such as preeclampsia and HELLP syndrome due to the similarity of symptoms and laboratory features. However, a timely suspicion of AFLP is crucial for offering prompt diagnostic work up, delivery and intensive supporting care preventing deleterious maternal and neonatal outcomes. To date, applying the Swansea criteria reflects the best diagnostic strategy to identify AFLP. However, applying these criteria may delay the diagnosis of AFLP since they seem to be most efficient when the disease is already in an advanced state and life-threatening complications are occurring.[22] Our data demonstrate that an s-Flt1 value >31100 pg/ml may be an additional parameter, if not even a key criterion, besides the Swansea criteria, to focus our attention on the differential diagnosis of AFLP. We postulate that sFlt-1 levels may herald AFLP prior to the presence of the Swansea criteria and before the patient is already severely ill. This gain of time may allow a coordinated peripartal management in a multidisciplinary setting.

Elevated sFlt-1 serum levels have been observed also in various non-obstetrical clinical situations including liver diseases.[23] Our findings of very high sFlt-1 values in AFLP patients may be explained by the enormous inflammatory stimulus involving various organ systems leading to proteinuria and altered blood pressure. This common pathomechanism involving sFlt-1 may explain why AFLP share similar features with preeclampsia and in particular with HELLP syndrome, which in turn delay the diagnosis or the differentiation of these pregnancy complications.

Strength and Limitations:

One major strength of our study is the strict use of inclusion criteria. Only patients matching all Mississippi or Tennessee criteria for HELLP syndrome were included in our study. Additionally, AFLP was only diagnosed when at least six Swansea criteria out of 15 were present. A limitation is the relatively small sample size of cases with AFLP. However, considering the rarity of the disease and the striking difference in particular of sFlt-1 between the groups we are confident that our findings together with the observation by Suzuki et al and Neuman et al. may elucidate that pregnancies compromised by AFLP show a different angiogenic pattern compared with other liver-associated pregnancy complications. Despite the enormous effort, prospective studies are eagerly needed to corroborate our findings.

Conclusion

A very high sFlt-1 serum level in pregnancy should focus our attention beyond preeclampsia; particularly on other liver-associated complications such as AFLP. Further studies are urgently required to investigate

whether angiogenic factors will become a helpful diagnostic tool to distinguish AFLP from other liver-associated pregnancy diseases.

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Disclosure of Interests

The authors declare that they have no competing interests.

Contribution to Authorship

FT was involved in collecting the data and analyzing the data.

LR (Luigi Raio) was involved in experimental planning, analyzing the data and writing the manuscript

AS was involved in analyzing the data and editing the manuscript

JCA performed the measurements of the biochemical factors

LR (Lorenz Risch) performed the measurements of the biochemical factors and optimized the assay

BM was involved in editing the manuscript

MF gave crucial intellectual inputs and edited the manuscript

MB planned the experimental design, analyzed the data, and wrote most of the paper.

Details of Ethics Approval

The study was approved by the institutional ethics committee of the canton of Bern (Kantonale Ethikkommission Bern, Ref.-Nr.: 365/15).

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References

1. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol. 2013* ; **170** , S. 1-7.

2. Magee LA, van Dadelszen P. State-of-the-art diagnosis and treatment of hypertension in pregnancy. *Mayo Clin Proc. 2018* ; **93** , 11, S. 1664-1677.

3. Tranquilli AL, Dekker G, Magee L, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. Pregnancy Hypertens. 4, 2014, S. 97-104.

4. Westbrook RH, Dusheiko G, Williamson C. Pregnancy and liver disease.*Journal of hepatology 2016* ; **64** , S. 933-945.

5. Liu J, Ghaziani TT, Wolf JL. Acute fatty liver disease of pregnancy: Updates in pathogenesis, diagnosis and management. *AM J Gastroenterology 2017* , S. 838-846.

6. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Preeclampsia.*Lancet 2010* ;. **376** , 9741, S. 631-44.

7. Nelson DB, Byrne JJ, Cunningham GF. Acute fatty liver of pregnancy.*Clinical Obstetrics and Gynecology 2020* ; **63** , 1, S. e152-164.

8. Churchill D, Duley L, Thornton JG, Moussa M, Ali HS, Walker KF. Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation. *Cochrane Database Syst Rev. 2018* Oct 5;10

9. Nelson DB, Yost NP, Cunningham FG. Acute fatty liver of pregnancy: Updates in Pathogenesis, Diagnosis and Management. Am J Obstet Gynecol. 209, 2013, 456, S. e451-457.

10. Minakami H, Morikawa M, Yamada T, Yamada T, Akaishi R, Nishida R. Differentiation of acute fatty liver of pregnancy from syndrome of hemolysis, elevated liver enzymes and low platelet counts. J. Obstet. Gynaecol. Res. 03 2014, 40, S. 641–649.

11. Knight M, Nelson-Piercy C, Kurinczuk J, Spark P, Brocklehurst P, UK Obstetric Surveillance System. A prospective national study of acute fatty liver of pregnancy in the UK. *Gut 2008* , **57** , S. 251-256.

12. Maynard SE, Min JY, Merchan J, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest. 2003* ; **111** , S. 649-658.

13 Verlohren S, Herraiz I, Lapaire O, Schlembach D, Moertl M, Zeisler H, Calda P, Holzgreve W, Galindo A, Engels T, Denk B, Stepan H. The sFlt-1/PlGF Ratio in Different Types of Hypertensive Pregnancy Disorders and Its Prognostic Potential in Preeclamptic Patients. *Am J Obstet Gynecol 2012* ; **206** (1):58.e1-8

14. Zeisler H, Llurba E, Chantraine F, Vatish M et al. Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. The New England journal of medicine. 374, 2016, S. 13-22.

15. Enengl S, Mayer RB, Le Renard PE, Shebl O, Arzt W, Oppelt P. Retrospective evaluation of established cut-off values for the sFlt-1/PlGF ratio for predicting imminent delivery in preeclampsia patients. *Pregnancy Hypertens. 2020* ; **19** :143-149.

16. Suzuki H, Nagayama S, Hirashima C, et al. Markedly higher sFlt-1/PlGF ratio in a woman with acute fatty liver of pregnancy compared with HELLP syndrom. J. Obstet. Gynaecol. Res. 45, 01 2019, 1, S. 96-103.

17. Neuman RI, Hesselink ERM, Saleh S, van den Meiracker AV, Danser AHJ, Visser W Angiogenic Markers Are Elevated in Women With Acute Fatty Liver of Pregnancy *Ultrasound Obstet Gynecol 2019* , **4**

18. Tranquilli AL, Brown MA, Zeeman GG, Dekker G, Sibai BM. The definition of severe and early-onset preeclampsia. Statements from the International Society for the Study of Hypertension in Pregnancy.*Pregnancy Hypertens. 2013* ; 44-47.

19. Hypertensive Prgnancy Disorders: Diagnosis and Therapy. Guideline of the German Society of Gynecology and Obstetrics (S2k-Level, AWMF-Registry No. 015/018, March 2019)

20. Barker ED, McAuliffe FM, Alderdice F, et al. The role of growth trajectories in classifying fetal growth restriction. *Obstet Gynecol 2013* ; **122** , S. 248-254.

21. Broere-Brown ZA, Schalekamp-Timmermans S, Jaddoe VWV, Steegers EAP. Fetal Growth and Placental Growth Factor Umbilical Cord Blood Levels.*Fetal Diagn Ther. 2018* ; **43** , 26-33.

22. Minakami H, Morikawa M, Yamada T, Yamada T, Akaishi R, Nishida R. Differentiation of acute fatty liver of pregnancy from syndrome of hemolysis, elevated liver enzymes and low platelet counts. *J. Obstet. Gynaecol. Res. 2014* ; **40** , S. 641–649.

23. Salcedo MX, Sanz-Cameno P, Medina J, et al. Association between angiogenesis soluble factors and disease progression markers in chronic hepatitis C patients. *Rev Esp Enferm Dig. 2005* ; **97** , 10.

FIGURE LEGEND

Figure 1: sFlt-1 serum levels in patients with HELLP syndromes or AFLP

Figure 2: PLGF serum levels in patients with HELLP syndromes or AFLP

Figure 3: sFlt-1/PLGF-ratio of patients with HELLP syndromes or AFLP

TABLE: Clinical characteristics of the study population

Clinical characteristics of women with AFLP or HELLP syndrome:

AFLP (n=6) HELLP (n=48) p-value

Maternal characteristics:

Age (years) 32 (24-37) 31 (20-40) NS, p=0.75

BMI (kg/m2) 23.5 (22-30) 24.5 (19-43) NS, p=0.87

Parity 1.5 (1-3) 1 (0-2) p<0.05

Nulliparity (%) 3 (50) 43 (89.6) p<0.05

Gestational age at sampling (weeks) 34.6 (31.7-39.1) 32.8 (20.4-39.3) NS, p=0.24

Neonatal outcome:

Cesarean section (%) 6 (100) 44 (91.7) NS, p=0.46

Gestational age at delivery (weeks) 34.6 (31.7-39.1) 32.8 (20.6-39.7) NS, p=0.3

Preterm delivery[1] (%) 4 (66.6) 39 (81.3) NS, p=0.40

Birthweight (grams) 2305 (1450-3445) 1522 (188-3240) p<.05

Birthweight percentile (%) 42.5 (18-58) 15 (1-75) p<0.05

FGR[2] (%) 0 (0) 23 (47.8) p<0.05

pH umbilical artery 7.23 (7.11-7.28) 7.33 (7.12-7.38) p<0.01

5 min APGAR score <7 (%) 3 (50) 9 (18.8) NS, p=0.08

NICU admission (%) 3 (50) 31 (64.6) NS, p=0.48

Values are shown as median (range), or number and % where appropriate;[1]*preterm delivery:* <37 0/7 weeks of gestation; [2]*FGR:* Fetal growth restriction defined by abdominal circumference <5th percentile / fetal weight <10th percentile with altered hemodynamic or abnormal growth trajectory over time; *NS:* not significant