Archives of Gynecology and Obstetrics (2019) 299:1557–1566
https://doi.org/10.1007/s00404-019-05128-6

MATERNAL-FETAL MEDICINE

Pilot study: placental biomarker predictive capability (sFlt-1, PlGF and their ratio) of postpartum maternal outcome

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Received: 10 September 2018 / Accepted: 25 March 2019 / Published online: 5 April 2019

Abstract

Background Prenatal measurement of placental biomarkers was able to improve screening and diagnosis of preeclampsia. Little is known about the clinical role of placental biomarkers in the postpartum period.

Methods This study is a prospective monocentric trial that included a total of 30 women with preeclamptic pregnancies. Serum placental biomarkers including soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF) were measured before and 2 h after delivery by Enzyme-Linked Immunosorbent Assay (ELISA) using commercially available kits according to manufacturer's instructions and correlated with the postpartum outcome.

Results Postpartum higher serum PlGF level was associated with postpartum elevation of the systolic blood pressure. Yet, the placental biomarkers were not able to predict general worsening of postpartum preeclampsia or other individual clinical or laboratory parameters.

Conclusion Serum concentrations of sFlt-1 and PlGF or their ratio in our study cohort did not completely predict the occurrence of postpartum preeclampsia. Yet, postpartum higher serum PlGF level was associated with postpartum elevation of the systolic blood pressure.

Keywords Postpartum preeclampsia · Placental biomarkers · PlGF · sFlt-1

Introduction

The placenta is crucial in normal and abnormal gestations [1]. Therefore, placental biomarkers have been subject of extensive research for the past decades. Increasing evidence highlight the effect of angio- and antiangiogenetic placental biomarkers throughout the whole gestation [2]. Physiological levels of placental angio- and antiangiogenetic factors are described in a series of publications [3]. In case of an antiangiogenetic predominance, the risk for developing preeclampsia increases. Two important placental biomarkers, the soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF), were shown to play central roles in the pathogenesis of gestational hypertensive diseases [4, 5].

One of the subtypes of vascular endothelial derived factors receptor-1 (VEGFR-1) is sFlt-1. This 100 kD molecular protein is produced by the placenta, causing anti-angiogenesis. Small amounts are also produced by monocytes and endothelial cells. Increased levels of this placental biomarker have been showed to increase the possibility of pre-eclampsia and intrauterine growth restrictions [6].

A vascular endothelial derived growth factor (VEGF) is the PlGF. The 30 kD angiogenetic protein is produced mainly in the placenta, but also in endothelial cells, natural killer cells, bone marrow and keratinocytes. Decreased levels of this placental biomarker have been documented in preeclamptic gestations [2].

In order to predict preeclampsia, the above mentioned placental biomarkers are incorporated in prenatal screening programs during the first, second and third trimesters [7–22]. If the biomarker standardized algorithm indicates an increased risk of preeclampsia during the first trimester; then prophylactic low-dose aspirin was shown to decrease the

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incidence of preeclampsia [23]. An increased sFlt-1/PlGF ratio in the second and third trimesters expresses the predominant antiangiogenetic placental function and is included in the diagnostic algorithms for preeclampsia. Patients may be thereafter directed to the appropriate health care facilities. By properly referring a high-risk pregnancy to a suitable health care unit, one can decrease complications occurring in an unprepared clinical setting [8, 9, 12, 18, 19, 24, 25].

The only known curative treatment of preeclampsia remains the termination of pregnancy. Yet, postpartum improvement, persistence or worsening of pre-eclampsia may attribute to the maternal morbidity and mortality, especially in unprepared clinical settings [26]. Despite huge amounts of evidence of placental biomarkers' significance in prenatal screening and diagnosis of preeclampsia, little is known about postpartum predictive roles of placental biomarkers. The risk for developing eclampsia increases in the first 48 postpartum hours in certain patients [27]. In addition to that, postpartum complications may follow mild preeclampsia, where the medical team is not expecting a complication [26]. To this date, there are no known methods to predict the postpartum maternal outcome.

In our study we assess the predictive value of placental biomarkers (sFlt-1, PlGF and their ratio) to estimate the postpartum short term maternal outcome.

Patients and methods

We conducted a monocentric prospective cohort study to evaluate the capability of placental biomarkers in predicting preeclamptic pregnancies' postpartum maternal outcomes.

Ethics statement

Ethical statement for this study was provided by the local Ethic Committee (Reference number: 249/13). All blood samples were obtained from individuals after signing a written consent that is approved by the ethical committee.

Study population

We enrolled preeclamptic pregnancies delivering in the department of obstetrics and gynecology of the University of Saarland Homburg. All subjects gave their written, informed consent before participation. Background data on the patients were provided by our electronic patient registry. A total of 30 individuals were recruited consecutively in the study.

Inclusion criteria were as follows: (1) diagnosis of preeclampsia according to the German national guideline for hypertensive diseases during pregnancy [26]; (2) gestational age between 23 + 5 and 41 + 6 weeks of gestation; (3) maternal age older than 18 years.

We excluded patients with chronic hypertension, chronic renal pathologies, nicotine abuse, multiple gestations, lupus erythematosus or other known autoimmune diseases, a maternal age of < 18 years or with language barriers.

Furthermore, we classified preeclampsia as mild and severe according to the same guideline [26]. A mild preeclampsia is defined as gestational hypertension accompanied with proteinuria of more than 300 mg. The hypertension had to newly occur after the 20th week of gestation. A severe preeclampsia is defined when additional renal, hepatic, pulmonary, hematological, hematological, fetal growth dysfunction or a blood pressure higher than 170/100 mmHg occurred. Also a early and late preeclampsia were defined as the occurrence of preeclampsia before and after 34 weeks of gestation. The birth percentiles were calculated according to the algorithm of Voigt et al. [28].

The postpartum maternal outcome was measured using the clinical and laboratory parameters. Once patients were recruited in the trial, clinical and routine laboratory parameters were assessed in a standardized manner. In addition to the routine surveillance, placental biomarkers (sFlt-1 and PlGF) were measured. Routine clinical parameters included symptoms suggestive of hypertensive crises or HELLP syndrome, e.g. headache, epigastric pain or neurological symptoms. Routine laboratory parameters included hemoglobin, platelet count, quick, INR, fibrinogen, uric acid, creatinine, liver enzymes, bilirubin, sodium and potassium. These parameters were measured prior to delivery, 2 h after delivery and on days 1–4 after delivery. The placental biomarkers (sFlt-1 and PlGF) were measured prior to and 2 h after delivery.

Our primary outcome was the correlation of the worsening of any of the maternal clinical and laboratory parameters with placental biomarkers. Clinical worsening was defined as the onset of one of the following: new symptoms suggestive of severe preeclampsia or HELLP syndrome, the elevation of the blood pressure by at least 10 mmHg, oliguria < 500 ml/24 h, occurrence of eclampsia, new onset of right sided upper abdominal pain, occurrence of persistent headache, occurrence of visual symptoms or the pathological development of laboratory parameter, i.e. hemoglobin or platelet fall, pathological renal, hepatic functions or coagulation profiles. For the worsening of laboratory parameters no quantitative thresholds were defined.

Our secondary outcome was a subgroup analysis, where we correlate each individual postpartum maternal clinical and laboratory parameter with placental biomarkers. We listed the maternal outcome above.

Tests of laboratory parameters

Routine laboratory parameters were performed in the University hospital's Central Laboratory.

Serum concentrations of PlGF and sFlt-1 were measured in our research laboratory by Enzyme-Linked Immunosorbent Assay (ELISA) using commercially available kits produced at R&D Systems® following manufacturer's instructions. Blood was collected in a standard serum tube: samples were centrifuged and stored at − 20 °C until analysis. Human PlGF Quantikine ELISA Kit and Human VEGF R1/Flt-1 Quantikine ELISA Kit were used for testing PlGF and sFlt-1, respectively. All measurements were performed in duplicate. The optical density was measured at 450 nm and referenced to 570 nm on a 96-well microplate reader (Sunrise-Tecan, Life Science). PlGF and sFlt-1 concentrations were obtained with a four-parameter logistic curve fitted against a standard curve and multiplied by the dilution factor using Magellan 7.2 Ink Data Analysis Software (Life Science-Tecan).

Statistical analysis

Following the intent-to-treat principle all patients included were analyzed. A two-sided comparison-wise significance level of 5% was used in this study as appropriate for exploratory studies. All continuous variables were analyzed using the descriptive statistics number of non-missing observations, mean, standard deviation, minimum, 1st quartile, median, 3rd quartile, and maximum.

The potential influence of the biomarkers on clinical worsening of symptoms was tested using a logistic regression with the event of interest as dependent variable and the biomarker as explanatory variable. The null hypothesis of no influence was tested against its alternative using the Wald test. The statistical analysis was performed using SAS version 9.4 software (SAS Inc. Cary, NC, USA sas.com).

Results

Study population

We recruited 30 patients for the trial after obtaining a written informed consent. 74% of the patients were primigravidae. The mean body mass index was 35.3 with a standard deviation of 9.0. The mean maternal age at the time of delivery was 32 years with a standard deviation of 4.9 years. The mean gestational age at the time of delivery was 33 weeks with a standard deviation of 4.3 weeks.

40% of the patients had mild, while 60% had severe preeclampsia at the time of delivery. In 23% of the cases HELLP syndrome complicated the pregnancy. Given the fact that most of the deliveries were preterm, the mean neonatal weight was 1930 g (18.6 centiles) with a standard deviation of 987 g (20.1 centiles). Table 1 presents the remaining results.

Overall 73% of the patients had an unfavorable maternal postpartum outcome, i.e. the pre-eclamptic signs, symptoms and complications persisted or worsened after delivery. 50% of the preeclamptic patients had postpartum worsening of signs and symptoms or witnessed the occurrence of new postpartum complications, e.g. development of postpartum HELLP syndrome, increasing hypertension.

Further descriptive analysis are presented in Figs. 1, 2, 3 and 4.

Postpartum predictive power of the absolute levels of sFlt-1, PlGF and their ratio at 2 h after delivery

In one setting we measured the absolute levels of the placental biomarkers immediately before and 2 h after delivery. We considered the absolute level of the placental biomarkers 2 h after delivery as a predictor for adverse postpartum maternal outcome.

Table 1 Clinical parameters of study population

Parameter	Mean	Std dev	Min	Lower quartile	Median	Upper quartile	Max
Maternal size (m)	1.7	0.05	1.6	1.6	1.7	1.7	1.8
Maternal weight (kg)	98.4	25.8	54.0	83.0	93.4	110.0	168.0
Maternal BMI	35.3	9.0	20.8	27.7	32.1	40.8	56.1
Maternal age (years)	32.1	4.5	24.00	29.0	32.0	34.0	43.0
Gestational age (weeks)	33.4	4.4	26.0	29.0	34.0	37.0	40.0
Apgar 1 min	6.9	2.1	3.0	5.0	7.0	9.0	9.0
Apgar 5 min	9.0	1.0	6.0	8.5	9.0	10.0	10.0
Apgar 3 min	9.3	0.9	6.0	9.0	9.5	10.0	10.0
Arterial neonatal (pH)	7.30	0.05	7.17	7.26	7.31	7.34	7.39
Birthweight (g)	1930	987	480	980	2030	2680	3880
Birthweight (centiles)	18.6	20.1	1	6	10	25.5	69

Data are presented as mean, standard deviation, minimal, median and maximal values with lower and upper quartiles

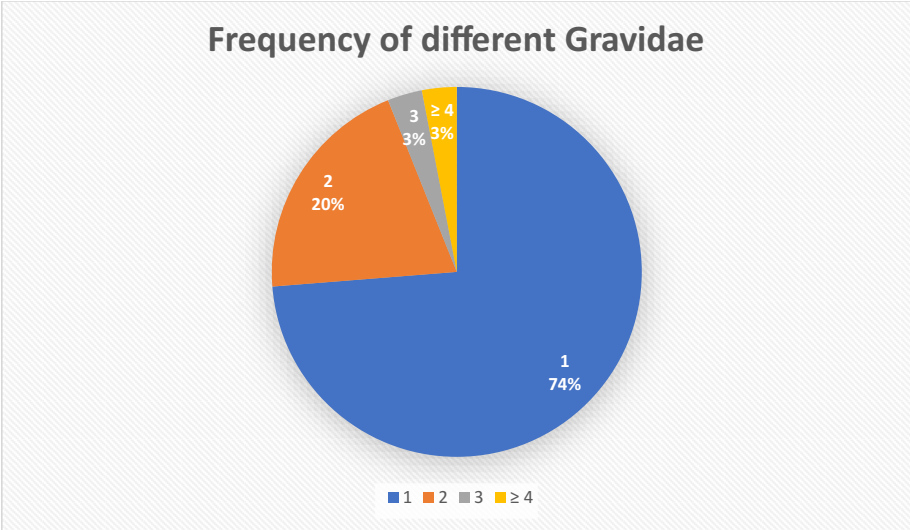

Fig. 1 Showing the frequencies of Gravida 1 (74%), Gravida 2 (20%), Gravida 3 (3%), ≥ Gravida 4 (3%)

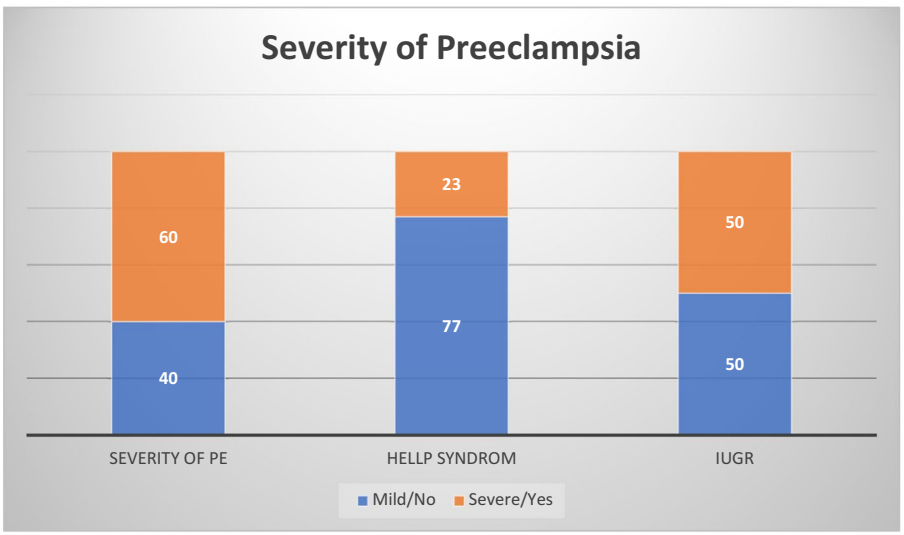

Fig. 2 Column chart describing the severity of preeclampsia in our patient collective. 60% had severe, while 40% had mild PE. 23% had HELLP syndrome and 50% had IUGR-fetuses

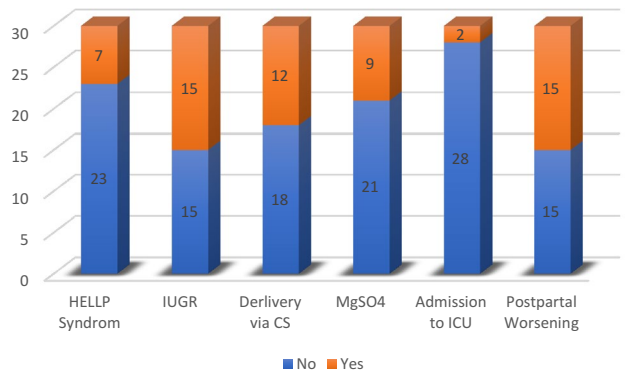

Fig. 3 Pre- and postnatal data description of the study population

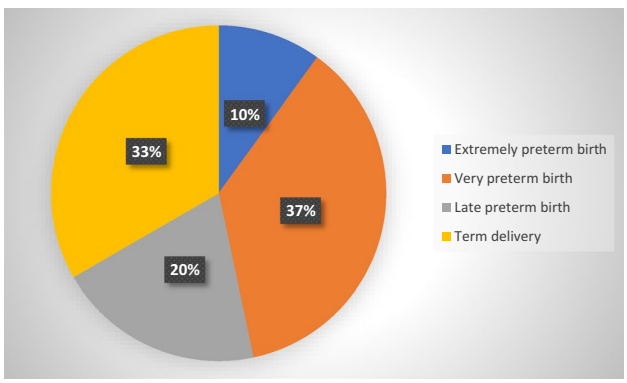

Fig. 4 Classification of gestation age at the time of delivery

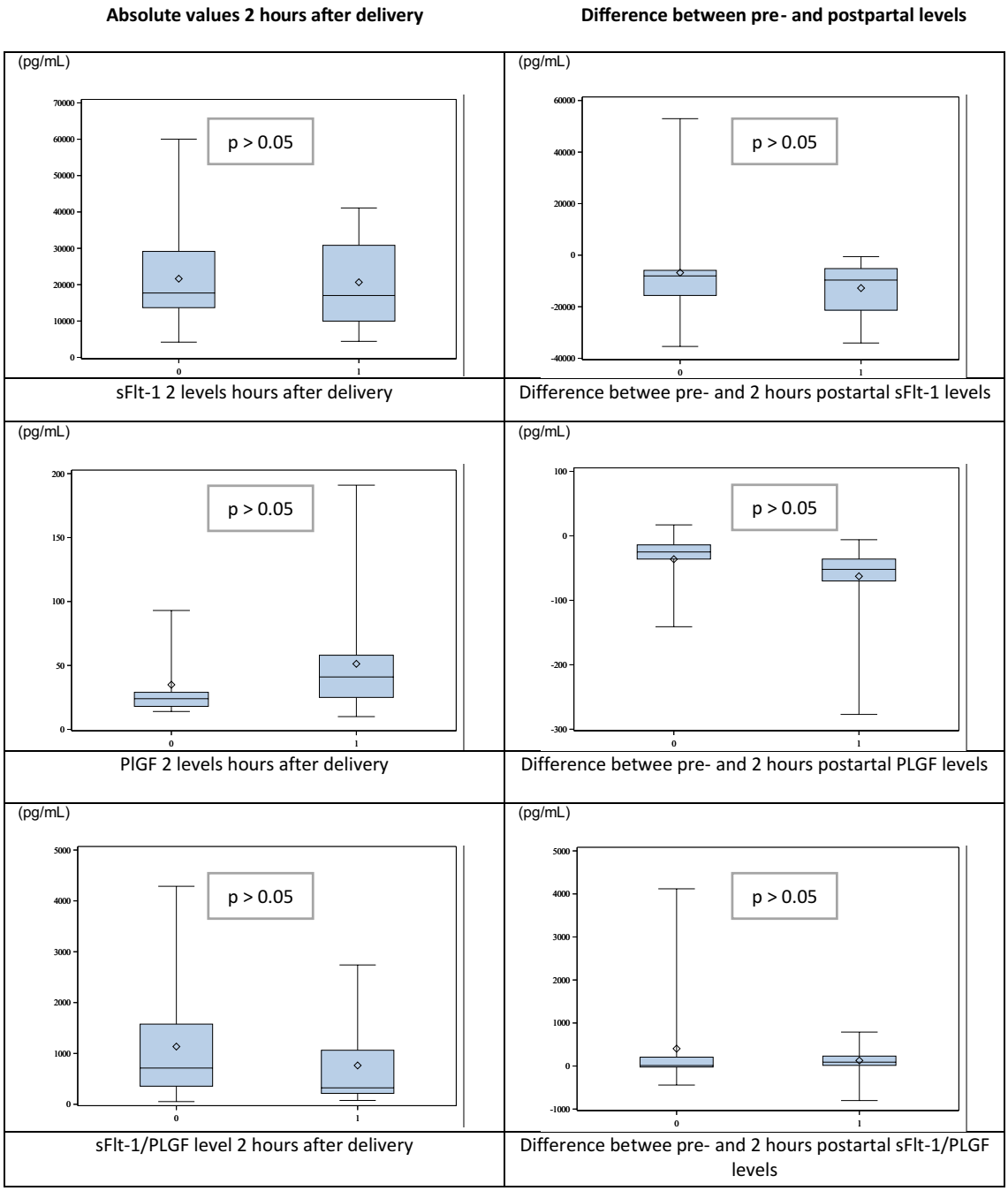

Fig. 5 Plot charts showing the predictive value of the biomarkers for postpartum maternal clinical worsening. A p value < 0.05 was considered statistically significant. Neither placental biomarker 2 h after delivery nor the difference between pre- and 2 h postpartum was able to predict the postpartum maternal worsening. In non complicated postpartal cases ($n = 15$), the prepartum sFlt-1, PlGF and their showed an average of 29,924.7 pg/ml, 70.2 pg/ml and 787.4, respectively. Postpartum sFlt-1, PlGF and their ration levels showed an average of 21,638.4 pg/ml, 34.9 pg/ml and 1145.0, respectively. In complicated postpartal cases ($n = 15$), the prepartum sFlt-1, PlGF and their showed an average of 33,421.5 pg/ml, 114 pg/ml and 636.4, respectively. Postpartum sFlt-1, PlGF and their ration levels showed an average of 20,659.8 pg/ml, 51.3 pg/ml and 763.8, respectively. In all graphs 0 and 1 stand for uncomplicated and complicated postpartal courses, respectively

Primary outcome

As presented in the plot charts in Fig. 5, the absolute values of sFlt-1, PlGF and their ratio were not able to predict postpartum general maternal worsening.

Subgroup analysis (secondary outcome)

Concentrations of PlGF were significantly higher in patients with worse daily mean of systolic blood pressure compared with patients who had stable daily mean of systolic blood pressure (see also Table 2, Fig. 6). The remaining parameters (postpartum elevation of the daily mean diastolic or mean arterial blood pressure, elevation of the maximal systolic, diastolic or mean arterial pressure, tachycardia, occurrence of adverse clinical symptoms, pathological changes of Na, K, reduction of the renal and hepatic functions or coagulation dysfunction) were not predicted using the absolute values placental biomarkers or their ratio as presented in Table 2.

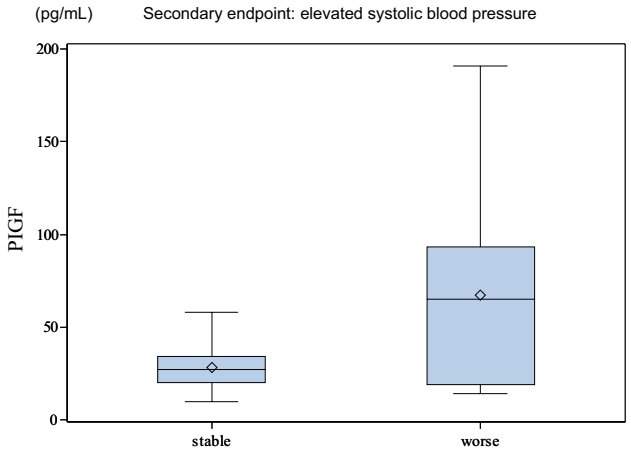

Fig. 6 Box plot showing a higher serum PLGF level in case of postpartal elevation of the systolic blood pressure (p value: 0.0239). The potential influence of the biomarkers on clinical worsening of symptoms was tested using a logistic regression with the event of interest as dependent variable and the biomarker as explanatory variable

Table 2 Laboratory demographics of the study population

	Mean	Median	St. deviation	Min.	Max.	Lower quartiles	Upper quartiles
Prenatal creatinine value	0.73	0.73	0.16	0.43	1.04	0.61	0.81
Creatinine 2 h after delivery	0.68	0.65	0.14	0.51	0.98	0.56	0.79
Prenatal uric acid value	6.0	5.9	1.5	2.9	9.0	4.8	7.2
Uric acid 2 h after delivery	6.6	5.8	4.2	2.9	27.0	4.9	6.9
Prenatal ALT	45	21	72	8	392	13	55
ALT 2 h after delivery	45	27	75	6	407	12	46
Prenatal AST	44	32	46	7	242	22	46
AST 2 h after delivery	44	32	47	14	266	21	45
Prenatal hemoglobin	12.3	12.3	0.7	11.1	13.5	11.7	12.7
Hemoglobin 2 h after delivery	11.5	11.5	1.1	9.6	14.0	10.7	12.1
Prenatal platelet level	206	195	89	62	407	146	285
Platelet level 2 h after delivery	192	174	71	52	348	139	249
Prenatal sFlt-1 level	31,673	27,186	18,841	5429	66,419	17,656	47,750
Prenatal PlGF level	92	73	78	16	385	40	118
Prenatal ratio	712	389	788	23	2657	170	923
sFlt-1 2 h after delivery	21,095	17,020	13,332	4193	60,015	11,794	30,543
PlGF 2 h after delivery	44	29	38	10	191	19	55
sFlt-1/PlGF ratio 2 h after delivery	929	565	1027	53	4287	215	1451
Prenatal INR	0.85	0.84	0.02	0.82	0.94	0.83	0.86
INR 2 h after delivery	0.85	0.85	0.03	0.81	0.99	0.84	0.86
Prenatal quick	97	100	18	1	100	100	100
Quick 2 h after delivery	96	100	19	1	100	100	100
Prenatal fibrinogen level	459	462	92	213	599	395	535
Fibrinogen level 2 h after delivery	419	409	96	198	567	350	500

Postpartum predictive power of the difference between the pre- and 2 h postpartum sFlt-1, PlGF serum levels and their ratio

In another setting we calculated the pre-partal and 2 h postpartum level difference of the placental biomarkers and their ratio (delta-sFlt-1, PlGF, ratio, respectively) to predict adverse postpartum outcome.

Primary outcome

As presented in Fig. 5, the pre-partal and 2 h postpartum level difference of sFlt-1, PlGF and their ratio were not able to predict postpartal general maternal worsening.

Subgroup analysis (secondary outcome)

The biomarker levels measured prior to delivery and immediately 2 h after delivery were not able to predict adverse postpartum changes as listed in Table 3.

Discussion

By means of the modern biomarkers of preeclampsia prior to and 2 h after delivery, we attempted to investigate whether these biomarkers can predict clinical and laboratory maternal postpartum outcome (Table 4).

Main outcome of our study

Neither the absolute serum value of sFlt-1, PlGF and their ratio, nor the follow-up of these placental biomarkers prior to and 2 h after delivery were able to predict the predict postpartum general maternal worsening. However, postpartum higher serum PlGF level was associated with postpartum elevation of the systolic blood pressure (p value 0.0239), as shown in Fig. 6.

Limitations

The limitation of our study is the small number of cases. Even though we could not establish a correlation between the angio- and antiangiogenetic maternal status and the postpartum maternal outcome, a bigger number of cases may

Table 3 p values of testing the influence of the absolute parameters of the placental biomarkers 2 h postpartum with respect to the postpartal maternal outcome

Maternal parameters 2 h after delivery	sFlt-1	PlGF	Ratio
Elevation of the daily mean systolic blood pressure	0.061	**0.0239**	0.0723
Elevation of the daily mean diastolic blood pressure	0.9466	0.2658	0.7735
Elevation of the daily mean arterial pressure	0.6872	0.5557	0.3951
Elevation of the daily maximal systolic blood pressure	0.61	0.4035	0.7760
Elevation of the daily maximal diastolic blood pressure	0.9041	0.3804	0.6028
Elevation of the daily maximal mean arterial pressure	0.6872	0.5443	0.2556
Elevation of the daily mean maternal pulse	0.8517	0.3503	0.6386
Occurence of a symptom suggestive of severe preeclampsia or HELLP Syndrome	0.5189	0.2347	0.7963
Elevation of the Na level	0.4493	0.8343	0.3869
Elevation of the K level	0.2715	0.5759	0.9075
Elevation of the creatinine level	0.1435	0.4589	0.2268
Elevation of the uric acid level	0.0511	0.2036	0.0395
Elevation of alanine aminotransferase (ALT)	0.7912	0.9215	0.6164
Elevation of aspartate transaminase (AST)	0.7322	0.26	0.1595
Reticulocytosis	0.5492	0.4264	0.9730
Hyperbilirubinemia	0.0981	0.9103	0.2027
Hemoglobin fall	0.1548	0.8575	0.7133
Platelet count fall	0.3316	0.4854	0.1873
Pathological INR	0.2806	0.4367	0.1963
Pathological quick value	0.1920	0.4854	0.3635
Lowering of the fibrinogen level	0.9880	0.9127	0.8673

Where the p value was < 0.05 (in bold), the 2 h postpartum biomarker showed statistically significant changes, thus is predictive for the given postpartum worsening. PlGF was able to predict 14 postpartum complicated systolic hypertension (average 48.2 vs. 44.5 pg/ml), while sFlt-1 showed a borderline significant change (average 14,619 vs. 23,228.3 pg/ml)

Table 4 *p* values testing the influence of the difference of pre- and 2 h postpartum placental biomarkers with respect to the postpartum maternal outcome

Maternal parameters 2 h after delivery	sFlt-1	PlGF	Ratio
Elevation of the daily mean systolic blood pressure	0.5087	0.1016	0.0586
Elevation of the daily mean diastolic blood pressure	0.8502	0.6154	0.8041
Elevation of the daily mean arterial pressure	0.7505	0.7368	0.4067
Elevation of the daily maximal systolic blood pressure	0.3345	0.2663	0.8678
Elevation of the daily maximal diastolic blood pressure	0.6144	0.4487	0.6198
Elevation of the daily maximal mean arterial pressure	0.4977	0.3635	0.2486
Elevation of the daily mean maternal pulse	0.5643	0.2188	0.7188
Occurence of a symptom suggestive of severe preeclampsia or HELLP Syndrome	0.1832	0.5874	0.7861
Elevation of the Na level	0.6888	0.1209	0.4648
Elevation of the K level	0.9493	0.6952	0.9050
Elevation of the creatinine level	0.3612	0.2091	0.2332
Elevation of the uric acid level	0.9284	0.3512	0.0384
Elevation of alanine aminotransferase (ALT)	0.7808	0.4357	0.6618
Elevation of aspartate transaminase (AST)	0.2441	0.3183	0.1509
Reticulocytosis	0.3753	0.5891	0.9867
Hyperbilirubinemia	0.5149	0.3267	0.2328
Hemoglobin fall	0.6150	0.7832	0.2562
Platelet count fall	0.7914	0.9171	0.6186
Pathological INR	0.8953	0.6038	0.2126
Pathological quick value	0.7726	0.6622	0.2799
Lowering of the fibrinogen level	0.2650	0.7581	0.4599

Where the p value was < 0.05, the serum level difference of the placental biomarker between pre- and 2 h postpartum showed statistically significant changes, thus is predictive for the given postpartum worsening

confirm or negate our findings more significantly. Due to the incidence of preeclampsia, a multicenter approach must be suggested to increase the number of cases. Yet, it has to be mentioned that the acute nature of preeclampsia hinders case recruitment. For the purpose of centrifuging and storing serum after delivery, the study team had to be present even in the middle of the night in the labor wards. This posed a big difficulty in obtaining the samples from all the patients.

The main aim of the trial was to detect the occurrence of postpartum worsening, in order to allocate proper resources where necessary. Therefore, we had to perform an early postpartum measurement of the biomarkers (2 h). According to Saleh et al. sFlt-1, PlGF and their ratios decrease rapidly and markedly after delivery, with an estimated half-life of 1.4 ± 0.3 days, of 3.7 ± 4.3 days, 0.6 ± 0.7 days, respectively, reaching a steady-state level of 77 pg/ml (range 52–3594 pg/ml), 9 pg/mL (range 4–24 pg/ml), 10 (range 6–274), respectively, i.e. corresponding to < 1, 30 and 2%, respectively, of the levels before delivery [24]. Despite of this fact, PlGF could predict according to our data and those of Noori et al. [29] the elevation of the mean arterial blood pressure 2 h and 12 weeks postpartum, respectively.

Given the consecutive nature of recruitment and the nature of the tertiary center, in which the study was performed, we had a high rate of severe preeclamptic patients. In our study population, the rate of severe preeclampsia was, therefore, twice as high as the mild preeclampsia, with a high rate of HELLP syndrome patients.

Biomarkers and risk of postpartum preeclampsia

In a series of earlier studies, it was suggested that an immediate postpartum curettage in preeclamptic patients can improve the maternal outcome [30–34]. In addition to these findings a curettage was followed by a drop in maternal serum sFlt-1 levels [35]. In a more recent prospective randomized trial a postpartum uterine curettage did not improve the postpartum maternal clinical or laboratory outcome [36]. Therefore, it could be suggested that even though the sFlt-1 levels drop following curettage, there is no direct correlation with the postpartum maternal outcome. This conclusion confirms our findings that the placental biomarkers do not predict the maternal outcome.

As shown in Fig. 6, postpartum higher serum PlGF level was associated with postpartum elevation of the systolic blood pressure. This interesting finding was indirectly shown by Noori et al. [29]. In their cross-sectional analysis, postpartum maternal serum PlGF levels were higher in women who had preterm preeclampsia, term preeclampsia and gestational hypertension when compared with patients

with normotensive pregnancy. These patients also continued to have a higher mean arterial blood pressure than women who had completed a normotensive pregnancy 12 weeks postpartum. Their and our findings strengthen our assumption of a possible predictive role of postpartum PlGF levels for postpartum maternal worsening. This effect needs to be studied further.

One possible explanation for the ability of PlGF to predict postpartum worsening unlike sFlt-1 could be the postpartal half-life. While sFlt-1 drops by 99% after the birth, PlGF decreases only to 30% of its gestational level [37]. PlGF even showed an initial postpartum increase in some patients before it declined. This could be explained by the decreased postpartum half-life of sFlt-1 compared to PlGF. It could be also explained by rapid postpartum decrease of sFlt-1 levels, as only free PlGF was measured using similar assays [24].

In another prospective, single center study, the postpartum kidney function was correlated 6 and 12 months after pregnancy in 44 preeclamptic patients and 9 healthy controls with prepartum sFlt-1 and PlGF serum levels. High prepartum sFlt-1 levels correlated with impaired renal function parameters in their collective. The study group concluded that prepartum sFlt-1 is a sensitive marker for impaired renal function postpartum. Yet, it is not sufficient enough to predict renal impairment after preeclampsia [25]. However, the study group did not analyze immediate postpartum maternal outcomes.

Differential diagnosis for postpartum persistence or worsening of the clinical picture

There are other reasons that can lead to the persistence or worsening of symptoms and signs of preeclampsia. Large volumes of fluids, regional anesthesia, delayed mobilization, nonsteroidal analgesics (e.g. Ibuprofen, indomethacin) and phenylpropanolamine or ephedrine may increase blood pressure. Preexisting renal diseases, hyperthyroidism or renal artery stenosis could also cause worsening of the clinical picture of preeclampsia [27]. Systolic and diastolic blood pressure values increase during labor. A systolic pressure ≥ 150 mmHg or diastolic pressure > 90 mmHg increases the risk of persistence or worsening of postpartum preeclampsia [38]. These variables elevate blood pressure using a different pathomechanisms; therefore, placental biomarkers may be unchanged. This may have affected the sensitivity of the placental biomarkers in predicting postpartum maternal outcome.

Conclusion

Despite that postpartum higher serum PlGF level was associated with postpartum elevation of the systolic blood pressure, the remaining placental markers did not completely predict the occurrence of postpartum preeclampsia. Yet, we further stress on value of predicting this maternal postpartum outcome following preeclamptic pregnancies.

Acknowledgements The authors would like to thank the Department of Obstetrics and Gynecology for providing the authors with the necessary logistical and financial support.

Author contributions AH: Conceptualization, methodology and project administration, validation of data and writing of the manuscript; CG: Statistical analysis; JCR: Formal analysis, reviewing and editing; EFS: Funding and supervising the project, reviewing and editing; JH: Recruitment, laboratory analysis; US: Conceptualization, Reviewing and editing; RB: Conceptualization, Reviewing and editing; RS: Data curation, reviewing and editing; ZT: Data curation, reviewing and editing; IJ: Reviewing and editing; RS: Reviewing and editing; GM: Reviewing and editing the manuscript; MK: Conceptualization, formal analysis, methodology, reviewing and editing the manuscript.

Funding The study and manuscript were funded by the Department of Obstetrics and Gynecology, University of Saarland.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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