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The immature platelet fraction in hypertensive disease during pregnancy

Ulrike Bernstein[1] · Thorsten Kaiser[2] · Holger Stepan[1] · Alexander Jank[1]

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Abstract

Purpose The aim of our study was to elucidate the role of IPF in preeclampsia, because the immature platelet fraction (IPF) is available in most emergency departments. A number of parameters have been introduced to diagnose preeclampsia/HELLP syndrome. The defined cutoffs of angiogenic and antiangiogenic parameters, soluble fms-like tyrosine kinase 1 and placental growth factor, have been approved for clinical routine. However, these parameters need complex analysis and are expensive.

Methods The data of 69 pregnant women between 20 and 42 weeks of gestation were analyzed in this retrospective monocentric study. 28 of them had preeclampsia, HELLP syndrome or partial HELLP syndrome fitting the Tennessee criteria (study group 1). Furthermore, 41 normotensive pregnant women were included as controls (study group 2). In both groups the IPF was analyzed.

Results In this study, we demonstrated that the values of IPF were significantly higher in patients with hypertensive diseases than in normotensives, but could not distinguish between preeclampsia and HELLP syndrome. The absolute number of immature platelets of women with preeclampsia was significantly higher and those of HELLP syndrome were significantly lower than values of healthy women. The absolute number of immature platelets as well as mature thrombocytes helps to distinguish between HELLP syndrome and preeclampsia.

Conclusion IPF levels are higher in women with hypertensive pregnancy than in normotensive controls. They could be used to diagnose hypertensive diseases in pregnancy. To distinguish between preeclampsia and HELLP syndrome, thrombocytes or the absolute number of immature platelets is needed.

Keyword Preeclampsia · HELLP syndrome · Immature platelet fraction (IPF)

Introduction

Hypertension is a frequent cause of maternal and fetal morbidity and mortality in pregnancy. About 2% of all pregnant women develop preeclampsia [1]. The incidence has increased by about 25% during the last two decades [2]. Preeclampsia is defined as new onset of hypertension at or after 20 weeks of gestation (> 140/90 mmHg) and proteinuria (> 300 mg/24 h) [3]. Early-onset preeclampsia is defined as onset before 34 weeks of gestation, and after 34 weeks it is called late-onset preeclampsia. Even if patients may not notice any symptoms initially, vision disorders, upper abdominal pain or headache might present at later stages [4].

HELLP syndrome is a severe manifestation of preeclampsia including hemolysis, elevated liver enzymes and low platelet counts. Different classifications exist to diagnose HELLP syndrome. The classification of the University of Mississippi includes thrombocytes lower than 150.000/µl, aspartate aminotransferase (ASAT) values higher than 40 IU/l (> 1.16 µkat/l) and lactate dehydrogenase (LDH) values higher than 600 IU/l. The criteria of the Tennessee-classification are stricter and include lactate dehydrogenase (LDH) values higher than 600 IU/l (> 10 µkat/l) and aspartate aminotransferase (ASAT) values higher than 70 IU/l (> 1.16 µkat/l) plus thrombocytes lower than 100.000/µl [5]. According to this classification, patients with partial HELLP syndrome meet at least one of these criteria.

In pregnancy, a modified platelet turnover can be observed. Although certain conditions like proteinuria,

✉ Alexander Jank
alexander.jank@medizin.uni-leipzig.de

[1] Department of Obstetrics, University Hospital of Leipzig, Liebigstr.20a, 04103 Leipzig, Germany

[2] Institute of Clinical Chemistry and Laboratory Medicine, University Hospital of Leipzig, Leipzig, Germany

arterial hypertension and dysregulation of vascular and endothelial markers can be observed in both preeclampsia and HELLP syndrome, changes in thrombocyte concentration, hemolysis, as well as elevated liver enzymes are pathognomonic for HELLP syndrome.

Despite diagnostic progress in finding pregnant women at risk for development or confirming subclinical preeclampsia, the pathophysiology of change in thrombocyte concentration and their function remains unclear. Until now, there are multiple screening parameters to diagnose preeclampsia at an early stage. Doppler parameters have been correlated with different additional blood serum parameters for a long time for the prediction of preeclampsia or intrauterine growth restriction. Lately, homocysteine has also showed value in this regard [6]. Recently, the use of angiogenic factors, soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PIGF), has been established. SFlt-1 is a soluble fragment of the vascular endothelial growth factor (VEGF). It binds PIGF and stops its antiangiogenic effect. Therefore, sFlt-1 operates strongly antiangiogenically [7]. Previous studies have demonstrated an increase in sFlt-1, as well as a reduction in PIGF weeks before manifestation of preeclampsia [8]. Placental dysfunction is considered to lead to a dysbalance between these angiogenic and antiangiogenic factors. Therefore, these parameters can be used to detect preeclampsia at an early stage. Recently, cutoffs have been determined. Verlohren et al. [9] established the cutoff sFlt-1/PIGF > 85 and after the 34th week sFlt-1/PIGF > 110. Furthermore, the sFlt-1/PIGF ratio could help in the prediction of disease progression and planning of management [10].

Other known parameters are soluble endoglin (sEng) and asymmetric dimethylarginine (ADMA) [11]. However, most of these parameters are expensive, need complex analyses and are difficult to standardize. Therefore, the determination of immature platelet fraction (IPF) may have a high potential for clinical practice.

Although new insights into the course of hypertensive diseases in pregnancy have been made, there is no causal treatment available yet. With antiplatelet medication, such as aspirin, only reduction of risk can be achieved. So far, the only way to protect the mother and child from consequential damage is delivery. Therefore, early diagnosis is needed to detect women at risk before maternal conditions arise. The rise in sFlt-1/PIGF has indicated a need for hospitalizing patients, but changes in short time interval laboratory parameters could be helpful in subclassification of preeclamptic women. For this, the regulation of bone marrow production could be observed from thrombocyte value. Especially reticulated thrombocytes, so-called immature thrombocytes, which are an intermediate form during thrombopoiesis, could reflect sudden crisis in estimating the bone marrow exhaustion. These platelets are larger and contain RNA in contrast to mature platelets [12]. The proportion of reticulated thrombocytes is also called immature platelet fraction (IPF). These immature platelets can be quantified by routine clinical hematology analyzers.

Little is known about the control of the physiological expenditure and depletion of platelets, which seems to be increased in pregnancies with hypertensive diseases. Reports of platelet production and decrease in normal pregnancy and preeclampsia suggest different values of platelet release [13]. Furthermore, platelet function seems to be altered. Here, platelet activation is thought to play the main role in the procoagulative condition during preeclamptic state [14].

Recent reference values already exist. In our own prospective study, we collected data and showed reference values of IPF in pregnancy. We could demonstrate for the first time in 207 serial and single measurements that the IPF in healthy pregnant women remains below 10%, and in most cases under 7–7.5% [15].

Our hypothesis is now that immature platelet fraction could be a useful parameter for antepartum and peripartum observance and may be of value in preventing complication like liver hematoma or more severe subcapsular rupturing or intracerebellar hemorrhage. While these complications are very rare, first of all the aim of our study is to find out whether IPF is different in women with preeclampsia and HELLP syndrome compared to normotensive women and to evaluate if it could be useful in diagnostics in a well- defined collective of patients with positive sFlt-1/PIGF ratio fitting the established clinical classification of Tennessee.

Materials and methods

After approval of the ethics committee (number: 336-13-18112013), pregnant women with suspected preeclampsia or HELLP syndrome as well as healthy women between 20 and 42 weeks of gestation were included in this single center study at the University of Leipzig Hospital, Department of Obstetrics, between 2013 and 2015. All women gave written informed consent. There were 204 women with suspected hypertensive diseases and 41 healthy women.

Women with preeclampsia and HELLP syndrome were defined as group 1. They presented with suspected hypertensive disease in pregnancy or with pain in the upper abdomen, sickness or headache. Their data were analyzed retrospectively. It was screened for the diagnostic criteria of HELLP syndrome or preeclampsia as previously described [3] as well as the sFlt-1/PIGF cutoffs [9]. Women with preeclampsia, HELLP or partial HELLP syndrome who did not meet the criteria were excluded. Of the 204 women who were suspected to have preeclampsia or HELLP syndrome, 28 pregnant women fit these criteria and could be included in the analysis. There were 7 women with early-onset and 7 women with late-onset preeclampsia as well as 14 women with HELLP syndrome. Women with preeclampsia were defined as group 1A. Patients with partial HELLP syndromes and HELLP syndrome were summarized into one group (group 1B). IPF (immature platelets in percent of all platelets), thrombocytes (/nl) and sFlt-1/PIGF were measured within 24 h after blood sampling. The first IPF value after diagnosis was included in all subjects. Women did not receive steroids. Before their pregnancy they had normal thrombocyte values (140–360/nl) and no preexisting hypertension. They were excluded if they had been given aspirin or heparin. Moreover, age, gravidity, parity and BMI were registered.

Healthy women were defined as group 2 (controls). A single blood sample was taken from 41 voluntary pregnant women who came for prematernity medical care. Blood samples were analyzed immediately. Secondary findings such as diabetes or hypothyroidism were documented. Furthermore, age, gravidity, parity and BMI were also registered. Patients were excluded if they had a disease which influenced thrombocyte function or number.

Summarizing, the data of 69 women were included in this study and analyzed. In both groups, the absolute value of immature platelets (immature platelets/nl) was calculated from IPF and mature thrombocytes.

All blood samples were analyzed by the XN 9000® (Sysmex, Kobe, Japan) at the Institute of Clinical Chemistry and Laboratory Medicine of the University of Leipzig. This analyzer contains a PTFL-channel to directly quantify immature platelets. Platelets were diluted with Cellpack DFL and then marked with Flurocell PLT (Sysmex Kobe, Japan) to stain RNA. Immature platelets could be identified by different intensity of fluorescence, due to a higher concentration of RNA, as compared to mature platelets [12].

IPF values, absolute values of immature platelets and thrombocytes of all groups were compared and analyzed with SPSS. Firstly, group 1A, 1B and 2 were statistically evaluated with the Kruskal–Wallis test to test whether the groups were significantly different. Afterward, the three groups were compared by Mann–Whitney *U* test against each other (1A against 1B, 1A against 2, 1B against 2).

Results

In our study, 69 pregnant women with a mean age of 29.54 years were included. There were 14 women with preeclampsia and 14 with HELLP syndrome after the defined criteria. In study group 1A, the mean age was 29.36 years, the mean gravidity 1.8, the mean parity 1.2 and the mean BMI was 23.1. In study group 1B, the mean age was 29.6 years, the mean gravidity 1.6, the mean parity 1.5 and the mean BMI was 24.7. In study group 2, the mean age was 29.6 years, the mean gravidity 1.9, the mean parity 0.6 and the mean BMI was 26.42.

Figure 1 shows the values of IPF in women with preeclampsia and HELLP syndrome compared to healthy women. Figures 2 and 3 show the absolute number of immature platelets and values of thrombocytes. All values presented are single measurements and each woman is represented once. Testing was performed with SPSS independently of weeks of gestation.

At first, IPF values were statistically evaluated with the Kruskal–Wallis test to test whether the groups were significantly different. According to this test, IPF was significantly different in women with HELLP syndrome, preeclampsia and in healthy normotensive women (median: HELLP 10.4%, preeclampsia 7.6%, healthy 4.1%, $p < 0.001$). The three groups were now compared by Mann–Whitney *U* test against each other. IPF values in patients with HELLP syndrome were significantly higher than in healthy pregnant women ($p < 0.001$). Furthermore, women with preeclampsia had significantly higher values of IPF than healthy pregnant women ($p = 0.004$). But if values of HELLP syndrome and preeclampsia were compared, they did not differ significantly ($p = 0.124$).

The Kruskal–Wallis test was also performed with the absolute number of immature platelets. They were significantly different (median: HELLP: 6.4/nl, preeclampsia: 16.7/nl l, healthy: 10.7/nl, $p < 0.001$). Compared with Mann–Whitney *U* test, the absolute values of immature

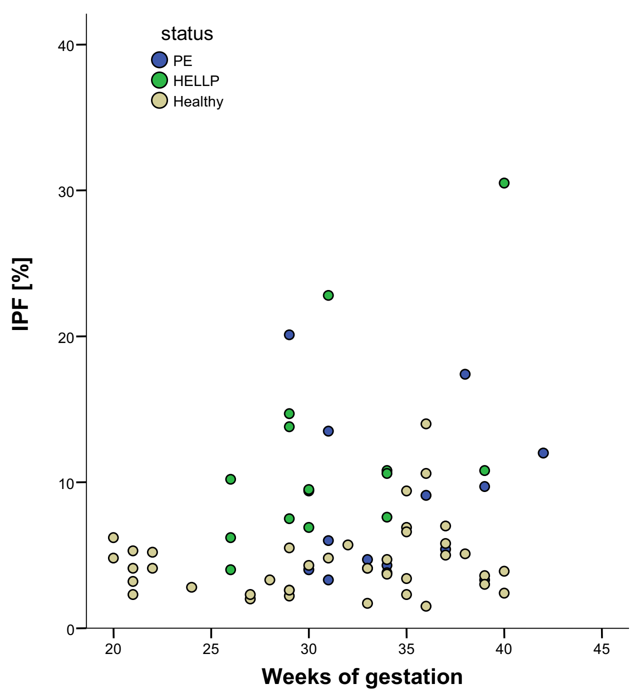

Fig. 1 IPF levels in percent on study group 1 and 2 from the 20th to 42nd week of gestation

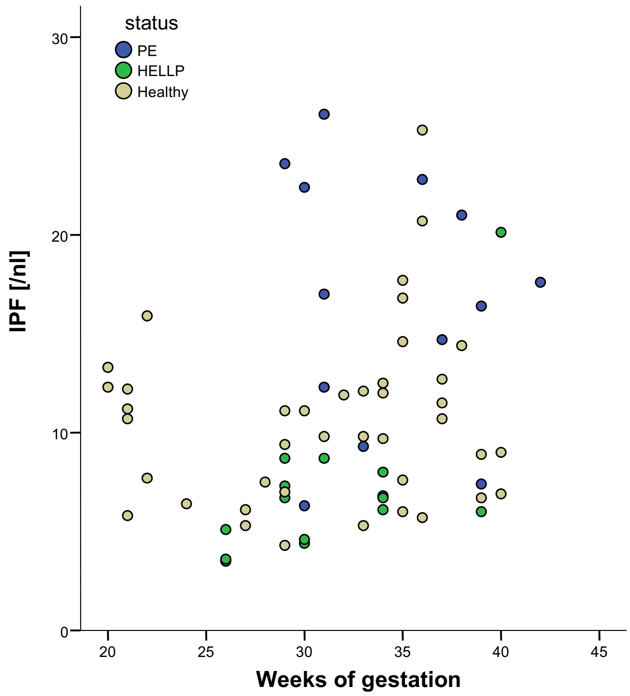

Fig. 2 Absolute number of immature platelets (/nl) in study group 1A, 1B and 2 from the 20th to 42nd week of gestation

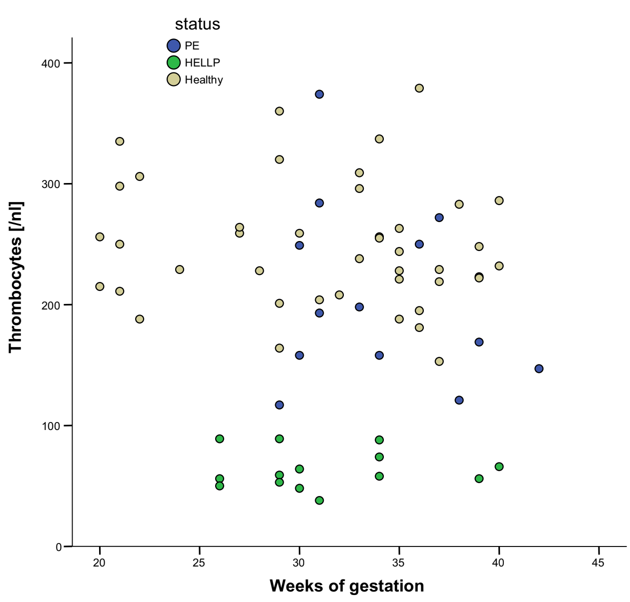

Fig. 3 Thrombocytes (/nl) in study group 1A, 1B and 2 from the 20th to 42nd week of gestation

platelets in patients with HELLP syndrome were significantly lower than in healthy pregnant women ($p = 0.002$). Furthermore, women with preeclampsia had significantly higher absolute values of immature platelets than healthy pregnant women ($p = 0.008$). Interestingly values of HELLP syndrome and preeclampsia differed significantly ($p < 0.001$) with lower values in HELLP patients.

The mature thrombocytes were also significantly different in the three groups in the Kruskal–Wallis test (median: HELLP: 59/nl, preeclampsia: 196/nl, healthy: 244/nl, $p < 0.001$). In the Mann–Whitney *U* test, the thrombocyte values of women with preeclampsia and HELLP syndrome were significantly lower than those of healthy women ($p < 0.001$). Thrombocyte values of women with preeclampsia were significantly lower than those of healthy women ($p = 0.03$). Thrombocyte values of women with HELLP syndrome were significantly lower than those of healthy women ($p < 0.001$) Thrombocyte values of women with HELLP syndrome and preeclampsia differed significantly ($p < 0.001$).

Table 1 shows patient characteristics of pregnant women with preeclampsia and HELLP syndrome. Table 2 shows the statistical data of all patients.

Discussion

The aim of our study was to elucidate the role of IPF in diagnosing preeclampsia. Until now, hypertensive disease in pregnancy is diagnosed with values of blood pressure, proteinuria and, in case of HELLP syndrome, with thrombocytes, LDH and ASAT. Recently, the use of sFlt-1/PlGF quotient has been established. Our study showed significant differences in values of IPF between normotensive pregnant women and women with hypertensive diseases such as preeclampsia and HELLP syndrome. Pregnant women with hypertensive diseases had significantly higher IPF values than normotensive controls. Whereas mean IPF values of women with normal blood pressure mainly remained below 7%, patients with preeclampsia and HELLP syndrome mainly had values higher than 10%. Our study showed different results considering absolute value versus the immature fraction of all thrombocytes (i.e., IPF). While IPF values were significantly higher in women with preeclampsia and HELLP syndrome, the absolute number of immature platelets was higher in women with preeclampsia but lower in women with HELLP syndrome compared to healthy women. Furthermore, IPF values showed no significant difference between preeclampsia and HELLP syndrome, whereas the absolute values of the immature forms and mature thrombocytes differed significantly. Thrombocyte values were lower in women with hypertensive diseases than in healthy women.

Moraes et al. compared the IPF of 34 pregnant women with preeclampsia with 33 normotensive pregnant women and 32 women with a hypertensive disease in pregnancy without proteinuria. In accordance with our findings, they found significantly higher values in pregnant women with preeclampsia than in those who were normotensive. Pregnant women with preeclampsia had a mean IPF of 8.6% and

Table 1 IPF characteristics of group 1A and 1B

Proband	Status	Age	BMI	Gravidity	Parity	Weeks of gestation	sFlt-1/PlGF	IPF (%)	Absolute value of IPF (/nl)	Thrombocytes (/nl)
1	PE	24	24.2	1	1	33	687.3	4.7	9.3	198
2	PE	28	34.3	2	1	31	539.91	3.3	12.3	374
3	PE	21	27.5	1	1	31	1377.33	6	17	284
4	PE	31	22.1	3	1	42	336.89	12	17.6	147
5	PE	33	20	3	2	30	530.9	4	6.3	158
6	PE	36	23.6	2	1	37	154.8	5.4	14.7	272
7	PE	22	18.8	1	1	39	204.98	9.7	16.4	169
8	PE	33	30.7	1	1	36	154.38	9.1	22.8	250
9	PE	35	30.5	2	1	29	344.09	20.1	23.6	117
10	PE	25	20	2	2	34	1343.63	4.3	6.8	158
11	PE	41	28	3	2	31	294.14	13.5	26.1	193
12	PE	39	21.3	2	1	38	140.55	17.4	21	121
13	PE	25	33.8	1	1	30	635.03	9.4	22.4	249
14	PE	18	18.6		1	39	165.81	3.3	7.4	223
15	HELLP	20	20.5		1	30	661.43	6.9	4.4	64
16	HELLP	30	22	1	1	26	989.96	6.2	3.5	56
17	HELLP	34	23.1	1	1	29	1214.54	7.5	6.7	89
18	HELLP	39	30.1	6	5	29	521.67	14.7	8.7	59
19	HELLP	26	19.4	1	1	34	506.61	10.8	8	74
20	HELLP	29	24.1	2	1	26	777.81	4	3.6	89
21	HELLP	24	23.6	2	2	31	1265.48	22.8	8.7	38
22	HELLP	29	29.4	1	1	29	372.45	13.8	7.3	53
23	HELLP	29	21.4	1	1	39	136.24	10.8	6	56
24	HELLP	34	32.8	3	3	34	279.77	7.6	6.7	88
25	HELLP	36	30.1	1	1	40	410.96	30.5	20.13	66
26	HELLP	18	20.8	1	1	26	1838.5	10.2	5.1	50
27	HELLP	35	21.2	1	1	34	186.88	10.6	6.1	58
28	HELLP	31	27.3	1	1	30	187.12	9.5	4.6	48

Table 2 Statistical data of group 1A, 1B and 2

	IPF (%)				Absolute value of immature platelets (/nl)				Thrombocytes (/nl)			
	Median	Minimum	Maximum	Standard deviation	Median	Minimum	Maximum	Standard deviation	Median	Minimum	Maximum	Standard deviation
Status												
PE	7.6	3.3	20.1	5.4	16.70	6.30	26.10	6.73	196	117	374	72
HELLP	10.4	4.0	30.5	7.1	6.40	6.40	20.13	4.12	59	38	89	16
Healthy	4.1	1.5	14.0	2.5	10.70	10.70	25.30	4.40	244	153	379	52

normotensives of 3.8%. Women with hypertension and no proteinuria had a mean of 7.3%. The difference between women with a hypertensive disease in pregnancy (with or without proteinuria) and those who were normotensive was significant ($p<0.001$) [16].

Everett et al. also highlighted increased values in pregnant women with preeclampsia compared to normotensive women. Their study included 10 women with preeclampsia compared to 10 with normal pregnancy and 35 female blood donors. Pregnant women were recruited in the third trimester and were adjusted for age with the normotensives. There was a significant difference in IPF between women with preeclampsia (3.8%, 9.6/nl) and normotensive pregnant women (0.9%, 3.4/nl, $p=0.01$). In contrast, there was no significant difference between normotensive pregnant women (0.9%, 3.4/nl) and non-pregnant (1.4%, 4.8/nl) female blood donors ($p = 0.29$) [12].

We assume from our data that absolute numbers of immature thrombocytes of women with HELLP syndrome are lower than those of healthy women, because the consumption of thrombocytes is higher. Therefore, in HELLP syndrome the relative immature platelet fraction of all thrombocytes is high but the absolute number of immature platelets shows bone marrow exhaustion, whereas in preeclampsia it is still able to compensate and in normal pregnancy bone marrow production of IPF is normal.

According to the results, IPF values showed significantly higher values in women with hypertensive diseases compared to normotensives, but could not distinguish between preeclampsia and HELLP syndrome. But absolute IPF values and thrombocytes could distinguish between the two significantly.

Based on our results, IPF measurement in percent could open new diagnostic possibilities in pregnancy. Since quantification by flow cytometry is easily available in most hospitals, IPF might also be of practical use in emergency diagnostics, as needed in hypertensive diseases. To distinguish between preeclampsia and HELLP syndrome, thrombocytes or absolute values are appropriate.

Limitations of our study are the small number of patients and the monocentric design. To create a clear and comparable cohort of patients, we decided to exclude them if they did not fit the Tennessee criteria and the sFlt-1/PIGF cutoffs. In clinical daily routine, these criteria are not used in each and every case. We used sFlt-1/PIGF-ratio to define the patient study group. The study of the correlation of this ratio with IPF or the absolute number of immature platelets in large patient numbers could be the aim of a future work to confirm our conclusions. It would be of very high interest if sFlt-1/PIGF and disease severity of preeclampsia/HELLP is correlated with bone marrow exhaustion. Further papers could also evaluate the difference between early- and late-onset preeclampsia in longitudinal series and comparison with healthy women where increase in IPF during pregnancy was shown [15]. To the best of our knowledge, we are the first to demonstrate the differences between absolute and relative values of immature platelets compared to mature thrombocytes in preeclampsia and HELLP syndrome. Because of the strict inclusion criteria, the relatively small number in the group and the retrospective character of the study, we could not perform longitudinal measurement in the single patient. Nevertheless, the results of the study indicate that a closer monitoring of IPF should be performed in longitudinal study design in severe cases of preeclampsia to estimate the value of measurement of IPF or absolute number of immature platelets in the course of severe preeclampsia and HELLP. Besides showing the functionality of bone marrow output in preeclampsia, this could improve clinical estimation of the risk of malfunction of platelet production and the risk of severe hemorrhage. While platelet consumption is a typical feature of HELLP syndrome, the differences in immature platelets in normal blood count and the abnormal relations of absolute and percentage of immature platelets are also measureable in preeclampsia without HELLP signs. When absolute immature platelet number is low under condition of low mature platelet count, the risk of more severe complications could be higher than in case of low platelet with working regulation of high immature platelet output of the bone marrow, reflecting existing reserve for new platelet production. For this reason, the measurement of bone marrow reserve by detection of immature platelet could correspond with quality of disease in hypertensive disease of pregnancy. There are no studies of IPF in case of liver hematoma or cerebral hemorrhage in hypertensive disease. Clinical management could be adapted in these rare cases when IPF or immature platelet count would be estimated precisely and severe bone marrow exhaustion diagnosed.

Authors' contribution UB: protocol/project development, data collection, data analysis, manuscript writing/editing. TK: data collection or management. HS: manuscript writing/editing. AJ: protocol/project development, data analysis, manuscript writing/editing/correcting and adding the revisions.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest relevant to this article.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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