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Changes of platelet count throughout pregnancy in women with antiphospholipid syndrome

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ABSTRACT

Objective: Antiphospholipid antibodies (aPL) activate several cell types, such as endothelial cells, monocytes, neutrophils, fibroblasts, trophoblasts and platelets, thus leading to thrombosis and obstetric complications in patients with antiphospholipid syndrome (APS). The aim of the present study was the longitudinal investigation of platelet count in women with APS. Additionally, platelet count in women with APS who developed preeclampsia during pregnancy were compared to women with APS and uncomplicated pregnancy for potential early detection of preeclampsia.

Material and Methods: This longitudinal study included 65 women with APS, 38 women with preeclampsia and 84 women with normal pregnancies, where platelet count was determined every four weeks, starting in early pregnancy.

Results: Platelet count was significantly lower in women with APS compared to women who developed preeclampsia and normal pregnancies starting at 12 weeks of gestation. The areas under the curve (AUC) for platelet count were 0.765 at 12 weeks of gestation (95% of CI of 0.634-0.896), 0.747 at 20 weeks (95% of CI of 0.600-0.894), 0.719 at 24 weeks (95% of CI of 0.555-0.882), respectively. The cut off points for platelets were 216 at 12-14 weeks of gestation, 226.5 at 20 weeks of gestation, and 163.5 at 24 weeks of gestation, respectively.

Discussion: We demonstrated a significant lower platelet count in women with APS throughout gestation. Additionally, platelet count is significantly decreased in women with APS who developed preeclampsia. According to our results, platelet count seems to have a predictive value for the development of preeclampsia in these women.

1. Introduction

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of antiphospholipid antibodies/aPl (anticardiolipin antibodies/ACLA, lupus anticoagulant/LA and anti-ß2-glycoprotein/anti-ß2-GPI) in the maternal circulation. These antibodies are associated with arterial and/or venous thromboses and with multiple adverse obstetric outcomes, such as early and recurrent fetal loss, preeclampsia (PE), intrauterine growth restriction (IUGR) and intrauterine fetal death (IUFD) (Miyakis et al., 2006). Thrombocytopenia is the most common non-criteria manifestation of APS, with a frequency of occurrence ranging from 20 to 50 % of cases (Cervera et al., 2002). APS occurs as primary APS (PAPS) or as secondary APS (SAPS) when combined with other autoimmune diseases such as systemic lupus erythematosus (SLE) (Lockwood et al., 1989; Pattison et al., 1993; Galarza-Maldonado et al., 2011; Asherson and Cervera, 2014; Gómez-Puerta and Cervera, 2014).

Antiphospholipid antibodies (aPL) activate several cell types, such as endothelial cells, monocytes, neutrophils, fibroblasts, trophoblasts and platelets (Pierangeli et al., 2006), thus leading to thrombosis and obstetric complications.

Beside prevention of bleeding, platelets seem to have an important role in immune responses and inflammation. Platelets are activated in APS and according to recent research, seem to be involved in the pathophysiology of these autoimmune diseases (Baroni et al., 2017).

Preeclampsia complicates about 10–17% of pregnancies with APS, as compared with 3–5% of pregnancies without this condition (Cervera et al., 2002; Levine et al., 2002; Clark et al., 2007). Preeclampsia in patients with APS is often severe and occurs early in pregnancy (Clark et al., 2007). It is characterized by an increased platelet consumption with consecutive reduction of overall platelet count and a consecutive rise in mean platelet volume (MPV).

The aim of the present study was the longitudinal investigation of platelet count in pregnant women with primary and secondary APS. Additionally, platelet count in women with APS who developed preeclampsia during pregnancy was compared to women with APS and

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Table 1
Demographic characteristics of all women included in the study.

	controls (n = 84)	APS (n = 65)	Non-APS preeclampsia (n = 38)	P
Age of patients (years)	32.91 ± 5.091	30.34 ± 5.64	32.97 ± 5.41	0.008
Pregnancy BMI	23.10 (21.18 - 27.38)	22.90 (20.45-25.90)	27.45 (20.88-33.60)	0.020
Average systolic blood pressure (mmHg)	122.12 ± 10.86	123.89 ± 12.31	148.97 ± 16.23	0.000
Average diastolic blood pressure (mmHg)	79.13 ± 9.83	78.46 ± 10.61	96.26 ± 11.30	0.000
Ethnicity				
African	0 (0.0%)	2 (3.1%)	3 (7.9%)	n.a.
Arabian	3 (3.6%)	4 (6.2%)	2 (5.3%)	
Asian	1 (1.2%)	0 (0.0%)	1 (2.6%)	
Caucasian	80 (95.2%)	59 (90.8%)	32 (84.2%)	
Antiphospholipid antibodies	–		–	n.a.
LA	–	28 (43.1%)	–	n.a.
ACLA	–	1 (1.5%)	–	n.a.
anti-ß2-glycoprotein	–	1 (1.5%)	–	n.a.
LA, ACLA	–	8 (12.3%)	–	n.a.
LA, anti-ß2-glycoprotein	–	0	–	n.a.
ACLA, anti-ß2-glycoprotein	–	12 (18.5%)	–	n.a.
LA, ACLA, anti-ß2-glycoprotein	–	15 (23.1%)	–	n.a.
Antiphospholipid antibodies (categorised)	–		–	n.a.
single positive	–	30 (46.2%)	–	n.a.
double positive	–	20(30.7%)	–	n.a.
triple positive	–	15 (23.1%)	–	n.a.
uterine doppler notch				
No	84 (100.0%)	42 (64.6%)	17 (44.7%)	0.000
Yes	0 (0.0%)	23 (35.4%)	21 (55.3%)	
IUGR				
No	84 (100.0%)	55 (84.6%)	17 (44.7%)	0.000
Yes	0 (0.0%)	10 (15.4%)	21 (55.3%)	
mode of delivery				
spontaneous delivery	51 (60.7%)	22 (33.8%)	7 (18.4%)	0.000
caesarean section	31 (36.9%)	41 (63.1%)	28 (73.7%)	
vaginally assisted	2 (2.4%)	2 (3.1%)	3 (7.9%)	

Data are presented as total numbers (%) or as means ± standard deviation, or in case of a skewed distribution as medians and interquartile range. n.a. not applicable
IUGR = Intrauterine growth restriction

uncomplicated pregnancy for potential early detection of preeclampsia.

2. Material and methods

We performed a secondary analysis of serum samples obtained during a prospective study of angiogenic factors in high-risk pregnancies (Mayer-Pickel K, et al. not published yet).

Data of 65 pregnant women with APS (24 primary APS, 41 secondary APS), 38 women without APS (group "non-APS preeclampsia), who developed preeclampsia (17 early onset and 21 late onset) and 84 pregnant controls who gave birth between January 2012 and December 2017 were included in this post-hoc analysis (Table 1). Women with APS fulfilled at least one of the Sydney clinical criteria (Miyakis et al., 2006; American College of Obstetricians and Gynecologists Committee on Practice Bulletins-Obstetrics, 2011).

None of the women with preeclampsia (group „non-APS"preeclampsia) in our study group had increased titers of antiphospholipid antibodies.

Adverse obstetric outcome was defined as recurrent early fetal loss, late fetal loss/intrauterine fetal death, intrauterine growth restriction (IUGR) or preeclampsia and H(hemolysis) EL (elevated liver enzymes) LP (low platelets)-Syndrome. Preeclampsia was defined as new onset of blood pressure ≥ 140/90 mm Hg on more than two readings taken 6 h apart after 20 weeks of gestation, combined with proteinuria ≥ 300 mg/24 h. In the absence of proteinuria, preeclampsia was defined as hypertension in association with thrombocytopenia (platelet count less than 100.000/microliter), impaired liver function(elevated blood levels of liver transaminases to twice the normal concentration), new development of renal insufficiency (elevated serum creatinine greater than 1.1 mg/dl or a doubling of serum creatinine in the absence of other renal disease), pulmonary edema, or new onset cerebral or visual disturbances (ACOG Committee on Practice Bulletins–Obstetrics, 2002).

Recurrent early fetal loss was defined as three or more consecutive miscarriages before 10 weeks of gestation; late fetal loss/intrauterine fetal death (IUFD) was defined as fetal death after 10 weeks; IUGR was defined as fetal growth < 5th percentile of gestational age.

Thrombocytopenia was defined as a platelet count of less than 150 G/l.

Controls were women without APS with uncomplicated pregnancies who had no signs of preeclampsia and delivered full-term healthy live births.

Inclusion criteria were singleton pregnancies and regular visits starting between 12 and 14 weeks of gestation. Exclusion criteria included multiple pregnancy, diabetes mellitus, coagulation disorders as well as any signs of active infection.

Women were recruited at time of admission for prenatal care, starting at 12 weeks of gestation.

Maternal venous blood samples (full blood count) were collected without anticoagulant at every routine visit, starting at early gestation (12–14 week of gestation) using vacuette tube. All samples were processed within 1 h after venipuncture, using an automatic blood cell counter (Sysmex XE 2100).

60 women (92.3%) with APS were treated with low dose aspirin/LDA and low molecular weight heparin/LMWH. 4 women (6.1%) did neither receive LDA nor LWMH, one woman (1.5%) recieved only LMWH. 17 women (26.2%) were treated with additional medications such as corticosteroids, azathioprine and hydroxychloroquine.

We excluded women who were lost in follow-up and whose records and blood samples were incomplete.

3. Antibody detection

IgG/IgM aCl and anti-ß2-GPI antibodies were assessed using commercial kits (Orgentec Diagnostika, Mainz/Germany). Lupus anticoagulans was assessed by multiple coagulation tests using platelet-poor plasma samples following international guidelines (Brandt et al., 1995;

Table 2
Clinical characteristics of 13 women with APS who developed preeclampsia.

	age	APS	aPl	medication	IUGR	uterine doppler notch	onset of preeclampsia	gestational age at time of delivery (weeks)	mode of delivery	neonatal outcome
patient 1	24	primary APS	LA	LDA, LMWH	yes	yes	early onset	27	c.s.	without pathological findings
patient 2	26	primary APS	triple positive	LDA, LMWH	yes	yes	early onset	29	c.s.	without pathological findings
patient 3	30	primary APS	LA	LDA, LMWH	no	no	late onset	37	c.s.	without pathological findings
patient 4	32	primary APS	triple positive	LDA, LMWH	yes	yes	early onset	32	c.s.	without pathological findings
patient 5	31	secundary APS	LA, ACLA IgG	LDA, LMWH, Corticosteroids	no	yes	early onset	34	c.s.	without pathological findings
patient 6	28	primary APS	triple positive	LDA, LMWH	yes	yes	early onset	24	spontaneous delivery	without pathological findings
patient 7	21	primary APS	LA	LDA, LWMH, apheresis	yes	yes	early onset	28	c.s.	without pathological findings
patient 8	28	secundary APS	LA	LDA, LMWH, Corticosteroids, HCQ	no	no	late onset	38	c.s.	without pathological findings
patient 9	33	primary APS	LA	LDA, LMWH	no	yes	late onset	40	spontaneous delivery	without pathological findings
patient 10	26	secondary APS	LA	LDA, LMWH	yes	yes	late onset	40	c.s.	without pathological findings
patient 11	30	primary APS	triple positive	None	yes	yes	early onset	27	spontaneous delivery	without pathological findings
patient 12	34	primary APS	LA	LDA, LMWH	no	no	late onset	40	c.s.	without pathological findings
patient 13	38	primary APS	LA	None	no	no	late onset	37	spontaneous delivery	without pathological findings

APS = antiphospholipid syndrome; LA = lupus anticoagulans; LDA = low dose aspirin; LMWH = low-molecular-weight-heparin; c.s. = caesarean section.

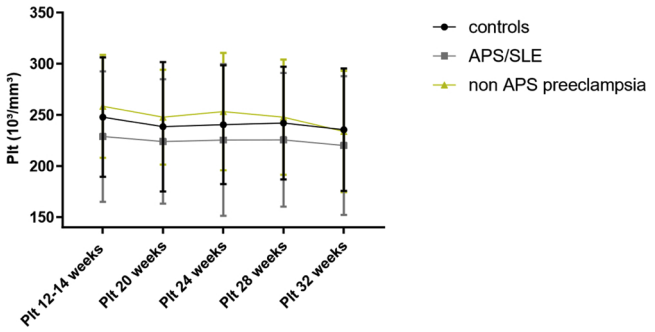

Fig. 1. Mean platelet count throughout gestation in women with normal pregnancies, APS and Non-APS preeclampsia.
Standard deviation (SD) is type of error depicted by bars

Pengo et al., 2009). Both tests were repeated after 12 weeks.

4. Measurement of platelet count

Platelet count was measured in coulter. Platelet count was measured in microscope in cases of platelet count below 100.000.

The study protocol (30–2011 ex 17/18) was approved by the Medical University Ethics Committee (IRB00002556).

5. Statistical methods

After data closure, all variables passed a plausibility check to detect outliers in the data set. No extreme values have been extracted from the full data set. Assumption of normal distribution was proved with Shapiro Wilk tests ($p > 0.05$ normally distributed data assumed) and Q-Q plots. If assumptions were met, one way ANOVA with Tukey correction was used for group comparisons according to clinical characteristics, otherwise non-parametric Kruskal Wallis tests have been applied using Bonferroni correction for multiple testing. Associations between categorical variables were analysed with Chi^2 tests. Time effects regarding the platelets (12–14 weeks up to 36 weeks) were tested after log transformation with repeated measures ANOVA, considered the between effect for the grouping (controls, APS, preeclampsia) and the interaction effect.

The receiver-operating characteristic (ROC) curves were generated to estimate the predictive ability for APS or for preeclampsia in the APS group for different parameters and time points. A value of 1.0 indicates that the features of the model perfectly separate patients with different outcomes while a value of 0.5 indicates the features contain prognostic information equal to have obtained by chance alone. Calculations of diagnostic points were based on the area under the ROC curves. Optimal cut-off levels were designed by the highest Youden Index to consider consequences of false positive and false negative predictions.

Data are presented as total number, as mean ± standard deviation, or in case of a skewed distribution, as median and Interquartile range (25-percentile and 75-percentile). Statistical tests were performed using SPSS version 23.0 (SPSS Inc., Chicago, IL). STATA version 12 (StataCorp LP, Texas, USA) and GraphPad Prism 7 (GraphPad Prism version 7.03 for Windows, GraphPad Software, La Jolla California USA) were used for visualisations. All tests were 2-sided with 95% confidence intervals (95% CIs). A p-value of less than 0.05 was considered as statistically significant.

6. Results

6.1. Description of the cohort

Demographic and clinical characteristics are shown in Table 1.

Pregnant women with APS were significantly younger than non-APS women with preeclampsia and healthy controls ($p = 0.008$) (Table 1a).

Non-APS women with preeclampsia had a a significantly higher BMI, as well as a significantly higher systolic and diastolic blood pressure at time of admission ($p = 0,0001$). The rate of IUGR and pathologic uterine artery Doppler studies with a bilateral notch was significantly higher in non-APS women with preeclampsia compared to women with APS and healthy controls ($p = 0,0001$) (Table 1).

13 women (20%) with APS (7 women before 34 weeks gestation/early onset preeclampsia and 6 women after 34 weeks of gestation/late onset preeclampsia) developed preeclampsia during pregnancy (Table 1b). 11 women (16.9%) developed preeclampsia despite treatment with LDA and LMWH (Table 1b).

Thrombocytopenia was found in 11 women (17%) of women with APS (8 women/72.7 % primary APS, 3 women/27.3% secondary APS), starting between 11 and 14 weeks of gestation (data not shown).

None of women with secondary APS developed a lupus flare during pregnancy; one woman with secondary APS developed a sinus venous thrombosis postpartum despite LMWH-therapy.

6.2. Platelet count of women with APS, non-APS women with preeclampsia and healthy controls

Platelet count was significantly lower in pregnant women with APS compared to non-APS women who developed preeclampsia and normal pregnancies at 12 weeks of gestation ($p = 0.005$), in pregnant women with APS compared to non-APS women who developed preeclampsia at 20 weeks of gestation ($p = 0.018$), in pregnant women with APS compared to non-APS women who developed preeclampsia and normal pregnancies at 24 weeks of gestation ($p = 0.020$) and in pregnant women with APS compared to normal pregnancies at 36 weeks of gestation ($p = 0.020$) (Table 2, Fig. 1).

6.3. Analysis of ROC curves for platelet count for prediction of preeclampsia in women with APS

The areas under the curve (AUC) for platelet count were 0.765 at 12 weeks

of gestation (95% of CI of 0.634-0.896), 0.747 at 20 weeks (95% of CI of 0.600-0.894), 0.719 at 24 weeks (95% of CI of 0.555-0.882), respectively (Table 3).

The ROC curves for platelet count are presented in Fig. 2. The cut off points for platelets were 216 at 12–14 weeks of gestation, 226.5 at 20 weeks of gestation, and 163 at 24 weeks of gestation, respectively, when the individual sensitivity (Sen) was 0.92, 0.92, 0.54, respectively. Their specificities (1-Spe) were 0.41, 0.50, and 0.12 and their Youden Indices were 0.52, 0.42, and 0.41 respectively (Table 3).

6.4. Platelets and antiphospholipid-antibodies

Pregnant women with APS who were triple-positive (LA, ACLA and anti-ß2-glycoprotein) had a significant lower platelet count compared to pregnant women who were single-positive or double-positive (Fig. 3).

7. Discussion

The main finding of the present study is a significantly lower platelet count at 12, 20 and 24 weeks of gestation as well as at 36 weeks of gestation in pregnant women with APS compared to non-APS women who developed preeclampsia and to healthy pregnant women. Although not statistically significant, platelet count was lower at 28 and 32 weeks in pregnant women with APS compared to non-APS women who developed preeclampsia and to normal pregnancies.

According to literature, aPl activate several intracellular signalling pathways in various target cells, such as platelets, endothelial cells, and trophoblasts, leading to cellular dysfunction with consecutive

Table 3
Area Under the Curve at different pregnancy weeks to analyse to optimal diagnostic points to predict preeclampsia.

	APS (n = 52)	APS Preeclampsia (n = 13)	Area	Standard Error	P	95% CI Lower Bound	Upper Bound
Plt 12-14 weeks (10^3/mm^3)	228.50 (180.00-269.50)	177.00 (146.50-206.00)	0.765	0.067	0.003	0.634	0.896
Plt 20 weeks (10^3/mm^3)	226.50 (186.25-247.25)	181.00 (130.50-218.00)	0.747	0.075	0.006	0.600	0.894
Plt 24 weeks (10^3/mm^3)	211.00 (181.00-265.00)	163.00 (127.00-219.50)	0.719	0.084	0.016	0.555	0.882
Plt 28 weeks (10^3/mm^3)	224.00 (187.50-258.50)	202.00 (150.00-211.00)	0.651	0.096	0.152	0.463	0.839
Plt 32 weeks (10^3/mm^3)	210.00 (172.00-265.00)	212.50 (185.00-276.00)	0.514	0.115	0.905	0.288	0.740
Plt 36 weeks (10^3/mm^3)	192.50 (169.00-224.75)	171.00 (161.25-197.25)	0.646	0.097	0.254	0.456	0.836
Plt 40 weeks (10^3/mm^3)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

	Diagnostic point	Sen	1-Spe	Youden index
Plt 12-14 weeks (10^3/mm^3)	216.000	0.923	0.404	0.519
Plt 20 weeks (10^3/mm^3)	226.500	0.923	0.500	0.423
Plt 24 weeks (10^3/mm^3)	163.500	0.538	0.118	0.421
Plt 28 weeks (10^3/mm^3)	213.500	0.889	0.442	0.447
Plt 32 weeks (10^3/mm^3)	183.000	0.143	0.294	0.151
Plt 36 weeks (10^3/mm^3)	175.000	0.667	0.325	0.342
Plt 40 weeks (10^3/mm^3)	n.a.	n.a.	n.a.	n.a.

CI = Confidence Interval; Sen = Sensitivity; Spe = Specificity.
Data are presented as median or interquartile range.
Standard error refers to area under the curve (AUC).

Fig. 2. ROC curves for platelet count to analyze the optimal cut-off points for predicting preeclampsia in pregnant women with APS.

Fig. 3. Antiphospholipid antibodies and mean platelet count.
Standard deviation (SD) is type of error depicted by bars

thrombosis, non-thrombotic vascular occlusion and obstetric complications (Meroni et al., 2011; Giannakopoulos and Krilis, 2013; Urbanus et al., 2008).

An association of low platelets and thrombosis has been demonstrated by various authors. Hisada R et al. have demonstrated a negative correlation of low platelet count ($< 150 \times 10^3$μL) and thrombosis in aPl positive patients, suggesting that a low platelet count might be a risk factor for developing thrombosis in these patients (Hisada et al., 2017). Rupa-Matysek et al. reported significantly higher MPV in aPl-positive patients with a history of thrombosis and/or pregnancy loss compared to aPl-negative patients with a history of thrombosis, suggesting that MPV might be used as a prognostic factor of thrombosis recurrence in patients with APS. However, platelet count did not differ between patients with and without APS (Rupa-Matysek et al., 2014).

Platelets seem also to be involved in the pathophysiology of obstetric APS (Schreiber et al., 2018 Jan). Sacharidou et al. have demonstrated that aPL-induced activation of various intracellular signalling pathways i.a. in platelets play an important role in fetal loss and placental dysfunction (Sacharidou et al., 2018).

It seems that, according to our results, women with APS have an increased platelet activation during pregnancy. However, only 17% of women with APS developed thrombocytopenia, independent of the development of preeclampsia.

We observed that women with triple positive aPl had a significant lower platelet count. As triple-positivity is associated with adverse obstetric outcome (De Carolis et al., 2018; Pengo et al., 2013), it might be speculated if a low platelet count might be a risk factor for various

complications during pregnancy in women with APS.

We and others have demonstrated that the sFlt-1/PlGF ratio might serve as an early potential screening parameter for the development of preeclampsia in women with APS (Qazi et al., 2008; Leaños-Miranda et al., 2015; Andrade et al., 2015; Kim et al., 2016; Bassyouni et al., 2012; Mayer-Pickel et al., 2018). Unfortunately, sFlt-1/PlGF ratio may not always be available. In such cases other predictive markers might serve as a first risk marker for preeclampsia.

Preeclampsia is characterized by an increased platelet consumption with consecutive reduction of overall platelet count and a consecutive rise in mean platelet volume (MPV).

Several authors have described the use of platelet count and MPV as potential predictive marker for preeclampsia (Chen and Lin, 2017; Mannaerts et al., 2017; Monteith et al., 2017; Kashanian et al., 2013; Kanat-Pektas et al., 2014; Freitas et al., 2013; Piazze et al., 2006; Yang et al., 2019; Yücel and Ustun, 2017; Özdemirci et al., 2016; Vilchez et al., 2017; Moraes et al., 2016; AlSheeha et al., 2016).

Han L et al. have investigated the use of various blood coagulation markers such as platelet count, MPV, partial thromboplastin time (aPTT), prothrombin time (PT), and thrombin time (TT) as potential biomarkers for the onset and severity of preeclampsia. The authors demonstrated that TT seems to be a reliable prognostic marker, whereas MPV is a potential marker for predicting the severity of preeclampsia at early gestation. Additionally, they noted a decrease of platelet count throughout gestation; however, they could not demonstrate any significant differences of platelet count between women with mild preeclampsia, severe preeclampsia and controls (Han et al., 2014). Tzur and Sheiner (2013) could not find an association of platelet count in first trimester and hypertensive disorders in late pregnancy, suggesting that platelet count might not be potential prognostic marker for the development of preeclampsia.

In our study, the ROC curve analysis showed that platelet count had the highest predictive values for preeclampsia until 28 weeks of gestation. We were able to identify a cut off point for platelet count of 216.0 at first trimester, 226.5 at second trimester and 163.5 at third trimester for the prediction of preeclampsia in women with APS. Although the AUC under the ROC curves for platelets are not very specious, they reveal significant class separation with an AUC between 0.765 and 0.719.

Our data are the first to compare platelet count in pregnant women with APS, non-APS women who developed preeclampsia and women with normal pregnancies, starting at first trimester. Additionally, we were able to demonstrate a positive correlation of platelet count and Triple positivity.

The limitations of the present study are the post-hoc design as well as the rather small sample size. Additionally, analysis of serum iron parameters such as ferritin and the association with platelet parameters would be of interest.

We demonstrated a lower platelet count in women with APS who developed preeclampsia, as early as 12 weeks of gestation and revealed that platelet count has a high predictive value until 28 weeks of gestation for the development of preeclampsia in these women.

In conclusion, platelet count seems to be a potential predictor for preeclampsia with clear cut-offs even at early gestation in pregnancies with APS. In case other predictive markers such as the sFlt-1/PlGF ratio may not be available, more attention should be drawn to risk markers that are easily accessible in order to predict preeclampsia and enable consecutive prophylaxis and early treatment in these pregnancies. Nevertheless, larger prospective studies are needed in order to confirm these pre-liminary results.

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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