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Early onset preeclampsia is associated with an elevated mean platelet volume (MPV) and a greater rise in MPV from time of booking compared with pregnant controls: results of the CAPE study

Abstract

Objective: To characterise Mean platelet volume (MPV) in patients with early onset preeclampsia (EOPE) and unaffected controls from time of first antenatal visit until the postpartum.

Materials and methods: Retrospective secondary analysis of an observational study in an Irish tertiary referral centre with 9000 deliveries annually. The MPV of 27 women with EOPE was compared to 19 unaffected controls. The inclusion criteria for the disease state was the development of EOPE defined by the National Institute for Health and Care Excellence (NICE) guideline, as new onset hypertension presenting after 20 weeks and prior to 34 weeks with significant proteinuria. Between October 2013 and July 2015 we recruited 27 women with EOPE and 19 pregnant controls. Statistical analysis was performed using paired T-test of Mann-Whitney test where appropriate and a P-value <0.05 was deemed significant.

Results: At time of diagnosis and late in the third trimester MPV was significantly increased to 9.0 (±0.3) fL in cases of EOPE in comparison to 8.5 (±0.6) fL in normotensive controls (P < 0.05). There was no significant difference during the first trimester or postpartum when comparing the MPV in EOPE to controls.

Conclusion: Despite an increased MPV at time of diagnosis of EOPE this study did not demonstrate a potential use for increased MPV as a first trimester screening tool.

Keywords: Platelets; prediction; preeclampsia.

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Introduction

Preeclampsia is a disorder of pregnancy characterised by the presence of hypertension (defined as a systolic blood pressure greater than 140 mm Hg or a diastolic greater than 90 mm Hg) and proteinuria (>300 mg/24 h period) emerging after 20 completed weeks of gestation [1]. Hypertensive disorders of pregnancy are thought to complicate approximately 10% of all pregnancies and preeclampsia is thought to affect between 2 and 8% of all pregnancies worldwide [2]. Despite an improvement in maternal outcomes, preeclampsia remains one of the leading direct causes of maternal deaths and is thought to be predominantly as a result of impaired placentation [3, 4]. A diagnosis of preeclampsia often coincides with a diagnosis of fetal growth restriction (FGR) and a resultant iatrogenic preterm delivery is a common consequence as the only curative treatment is delivery of the placenta. Early onset preeclampsia (EOPE) with onset prior to 34 weeks is a rare variant of the disease spectrum associated with a higher rate of maternal and fetal complications.

Although the precise aetiology remains poorly characterised, preeclampsia is a pro-inflammatory state associated with platelet and coagulation activation. As a result of this known association of thrombocytopenia with preeclampsia much of the research to date has involved investigating platelet function and responsiveness in the setting of preeclampsia. A rise in mean platelet volume

(MPV) which is associated with a reduction in overall platelet count is suggestive of active turnover of platelet production in bone marrow as a result of platelet consumption in preeclampsia [5–7]. MPV, is a sensitive indicator of platelet activation and consumption [8], and is a routine parameter reported on all full blood counts (FBC) in our institution. It is a simple and inexpensive test which has been performed as an indicator of a variety of clinical conditions such as myocardial infarction, sepsis, hyperthyroidism and acute exacerbation of chronic obstructive pulmonary disease [9–12]. The primary aim of this study is to compare the MPV of EOPE with unaffected controls during throughout the antenatal and postnatal period.

Materials and methods

Patients

The CAPE Study (Coagulation Activation in PreEclampsia) was a single centre prospective study conducted at one of the largest academic maternity centres in Ireland. The Rotunda hospital is a tertiary referral centre with 9000 deliveries annually. For the purpose of this study EOPE was defined as per the National Institute for Health and Care Excellence (NICE) Guideline as new hypertension presenting after 20 weeks and prior to 34 weeks with significant proteinuria [1]. Inclusion criteria included developing proteinuria and hypertension prior to 34 completed weeks of gestation. Exclusion criteria included significant medical comorbidities (documented renal disease, systemic lupus erythematous (SLE), proven autoimmune disease); a confirmed coagulation disorder or significant anaemia (patients with haemoglobin <70 g/L were excluded to avoid worsening of symptomatic anaemia by venesection). Between October 2013 and July 2015 the CAPE study approached and recruited women who were attending either the Rotunda Daycare Unit or were inpatients with EOPE. Pregnant controls were approached to participate and were matched with cases according to gestational age, maternal age and body mass index (BMI-defined as body weight in kg divided by height squared m²). All women were given a patient information leaflet and written consent was obtained prior to participation.

Sample collection and processing

All pregnant women in our institution have a full blood count (FBC) performed from a venous sample at their first antenatal visit. Venous blood was collected as part of routine booking bloods via a 22 Gauge needle into 3 mL vacutainers containing K3EDTA (VACUETTE® 3 mL K3E, K3EDTA, Greiner Bio-One International, Austria). Samples were routinely analysed in the Rotunda Hospital accredited laboratory on the same day within an hour of sampling via a fully automated haematology analyser (Cell-Dyn Sapphire, Abbott Core Laboratory, IL, USA). MPV at this first antenatal visit was retrieved from an electronic laboratory database. Study participants had routine venepuncture for the assessment of their disease state which included a repeat FBC

this again allowed for retrieval of the MPV from the electronic laboratory database.

Data collection

Information collected included demographic characteristics, smoking status, medical history, obstetric history, previous hypertensive disease, medications, current antihypertensive requirements, use of antenatal steroids and use of anti-platelet medications. MPVs were retrospectively retrieved from the electronic laboratory database and timing of collection was divided into the following time points: first antenatal visit, between 24 and 33 weeks gestational age (to coincide with EOPE diagnosis), between 34 and 40 weeks gestational age, day 2 – day 4 postpartum, day 5 – day 27 postpartum and greater than 28 days postpartum.

Statistical analysis

Statistical analysis were performed using SPSS version 22 (IBM Corporation, NY, USA) and GraphPad Prism (Horsham, PA, USA) statistics software. The results were considered statistically significant if $P < 0.05$.

Ethical considerations

The study protocol was assessed by the local ethical committee (Rotunda Hospital, Dublin, Ireland) and ethical approval was granted following review. All participants were given a patient information leaflet and had a required a good knowledge of English to give written informed consent prior to study participation. Following recruitment participants were assigned an anonymised study number. This research was carried out in accordance with the declaration of Helsinki.

Results

During the study period a total of 15,299 deliveries were recorded in our unit and of these 334 (2.2%) had a pregnancy complicated by preeclampsia. The majority (n = 294) were defined as late onset preeclampsia emerging at greater than 34 weeks gestational age and the remaining 40 women were classified as EOPE. Recruitment was not possible in two cases due to the severity of disease state and the brevity between clinical presentation and delivery. Of the remaining 38 women, 10 were excluded due to established exclusion criteria as detailed in the methods. This left a resultant 28 women who were eligible for participation and 27 of whom provided their written informed consent.

Table 1: Baseline demographic and clinical characteristics for cases and controls.

	n (%)/mean ± SD	
	EOPE (n = 27)	Control (n = 19)
Age (years)	35.1 ± 5.4	31.6 ± 5.3[a]
BMI (kg/m²)	29.2 ± 6.0	26.1 ± 5.5[a]
Risk factors		
Nulliparous	18 (66.7)	10 (52.6)
Pre-pregnancy HTN	6 (22.2)	0 (0)
Previous PET	2 (7.4)	0 (0)
DM/GDM	1 (3.7)	1 (5.3)
Smoker	1 (3.7)	2 (10.5)
Ethnicity		
White European	22 (81.5)	18 (94.7)
American	0 (0)	1 (5.3)
Asian	3 (11.1)	0 (0)
African	2 (7.4)	0 (0)
GA at diagnosis (weeks)	32.0 ± 2.0	N/A
SBP at diagnosis (mm Hg)	157 ± 16	N/A
DBP at diagnosis (mm Hg)	96 ± 7	N/A
Proteinuria	1.29 ± 1.29	N/A
GA at delivery (weeks)	32.9 ± 2.2	38.3 ± 2.8[b]
SBP at delivery (mm Hg)	163 ± 18	N/A
DBP at delivery (mm Hg)	99 ± 12	N/A
Birthweight (g)	1692 ± 611	3092 ± 607[b]
FGR	5 (18.5)	0 (0)
LSCS	27 (100)	9 (47.4)
EBL (mL)	458 ± 168	462 ± 220
PPH >1000 mL	1 (3.7)	1 (5.3)
HELLP	7 (25.9)	0 (0)
Eclampsia	0 (0)	0 (0)

EOPE = Early onset PET, PET = preeclampsia, HTN = hypertension, GA = gestational age, SBP = systolic BP, DBP = diastolic BP, DM = diabetes mellitus, GDM = gestational diabetes mellitus, FGR = fetal growth restriction, LSCS = lower segment caesarean section. Variables were compared using one-way ANOVA [a]$P < 0.05$, [b]$P < 0.0001$.

Twenty seven women with EOPE and a mean (±standard deviation −SD) age and BMI of 35.1 (±5.4) years and 29.2 (±6.0) kg/m², respectively were recruited. An additional 19 women with normotensive pregnancies and a mean age 31.6 (±5.3) years and BMI of 26.1 (±5.5) kg/m² were recruited as controls. Table 1 further illustrates the demographics of patients in both the EOPE affected and control states. In this study we did not demonstrate a significant difference in the MPV in the first trimester with a mean MPV between EOPE and controls of 8.1 (±1.7) fL and 8.1 (±1.1) fL, respectively. However, at time of clinical presentation of disease there was a significant increase in the mean MPV among EOPE patients 9.0 (±0.3) fL in comparison to normotensive controls 8.5 (±0.6) fL further detailed in Figure 1. This significant increase continued in the third trimester but surprisingly the increase in MPV with EOPE did not persist in

the postpartum period. In fact the MPV began to trend to less than that of the control cohort and from as early as day 2 postpartum as detailed in Figure 2.

Comment

This study has detailed that there is a significant increase in MPV at time of diagnosis of EOPE. However, we have not demonstrated a difference in MPV between EOPE and normotensive controls in either the first trimester or postpartum.

There were significant differences observed in the gestational age at delivery, FGR and birthweight. However, this is in keeping with EOPE as it tends to be a phenotypically "pure" with a more severe disease state requiring earlier delivery. Women with EOPE demonstrated an increased chance of Caesarean section delivery at 100% but despite an increased antenatal MPV this did not translate to an increased estimated blood loss at time of delivery. So despite the increased platelet turnover and immature platelets indicative by an increased MPV, platelet function may have been preserved.

A significant strength of this study was our ability to characterise a large proportion (>95%) of eligible women presenting with EOPE. This sample represents almost the entire EOPE cohort of this centre over the 2 year period (exclusion criteria not withstanding) and is therefore a true reflection of our hospital population. Despite the strength of our recruitment in recruiting the majority of EOPE patients in the 2 years. This study is limited by small numbers secondary to the expected low EOPE prevalence of 0.2%. In addition, to the small numbers reported in this study the observed differences in MPV whilst statistically significant was small and may not equate to clinical value. A larger trial would need to be repeated to assess the reproducibility and clinical relevance of our findings. We acknowledge that a further limitation of this study is that our control population did not have blood sampling completed at all time points. This was secondary to the uncomplicated nature of those pregnancies. In addition, assessment of MPV values with respect to ethnicity was not feasible in this analysis as all of our control group were Caucasian.

The MPV has gained recent interest as a potential marker and predictor for preeclampsia. However, an elevated MPV should be interpreted with caution as it has demonstrated to be influenced by both ethnicity, BMI and in the setting of gestational diabetes (GDM) [13, 14]. In contrast a reduction in MPV value has been reported by Ulkumen et al. [15] in pregnancies complicated by preterm labour.
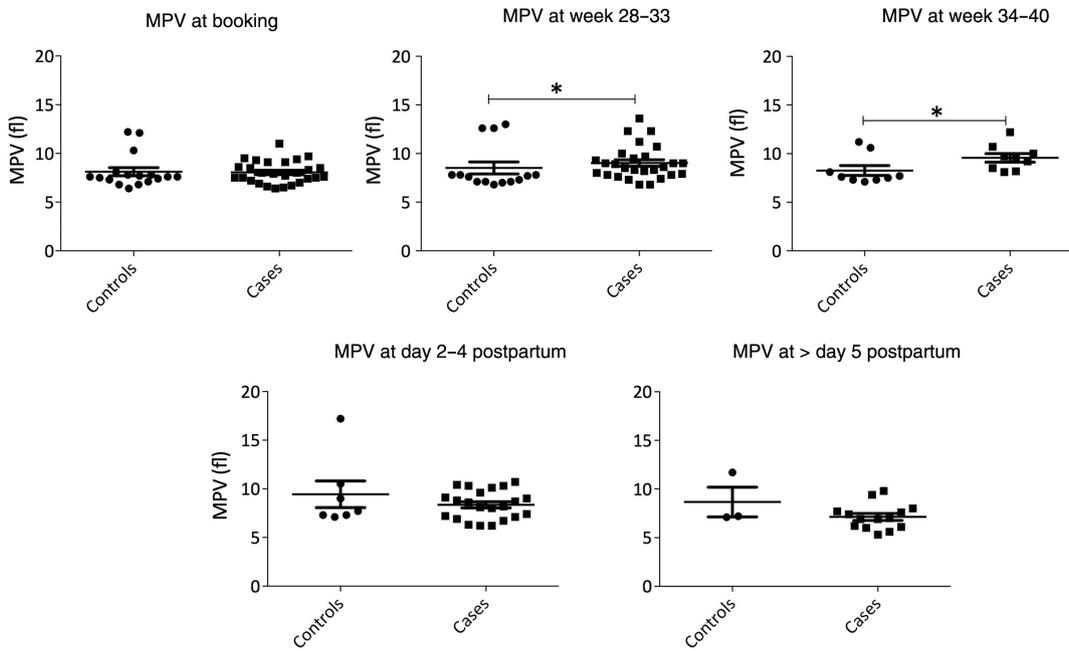
Figure 1: MPV spread of values from booking to postpartum.
Statistical analysis via prism graph pad using Mann-Whitney 2 tailed test *P < 0.05.
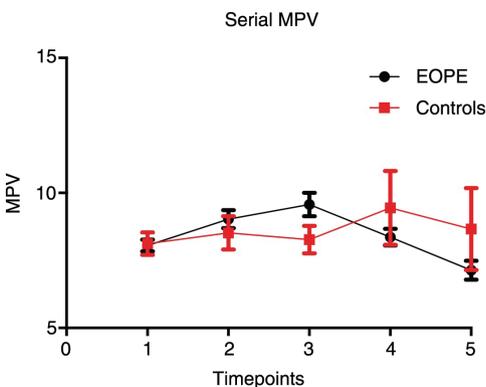

Figure 2: Serial trend in MPV in both EOPE and normotensive controls.
Time point (1)- booking visit; timepoint (2)- 28–33 weeks gestation; timepoint (3)- 34–40 weeks gestation; timepoint (4)- day 2- day 4 postpartum; timepoint (5)- greater than day 5 postpartum.

This study adds further to the conflicting evidence of the use of MPV in the first trimester for the identification of the pregnancy at increased risk for PET. As detailed in our results in the first trimester did not demonstrate any difference in the MPV between patients with EOPE and normotensive controls. This is in contrast to the findings of Myatt et al. [13] who demonstrated a significant increase in the MPV levels in the first trimester when comparing women with preeclampsia to unaffected controls. Whereas Gezer et al. [16] have reported that a women who subsequently developed preeclampsia had significantly lower levels of MPV than normotensive controls.

Similar to our findings there is a growing body of evidence confirming the significant association of an elevated MPV and preeclampsia when assessed in the second and third trimesters [17–25]. Despite this significant evidence both Saleh et al. and Yavuzcan et al. [26, 27] were unable to replicate these findings and in their studies they demonstrated that there was no significant difference in the MPV of preeclamptic women in comparison to normotensive controls. When assessing the role of MPV in distinguishing pregnancies complicated by gestational hypertension Karalis et al. and Ohshige et al. [28, 29] also reported no difference in MPV levels in women with gestational hypertension and normotensive controls. Longitudinal data extending to the postpartum is scarce and again poses conflicting results with the MPV parameter. A study by Jaremo et al. [30] has demonstrated a significant increase in MPV of women with preeclampsia in comparison to unaffected controls extended to the postpartum. We did not replicate those findings of an increase in postnatal MPV in our cohort but rather demonstrated a reduction in MPV in cases of EOPE 8.4 (±0.3) fL in comparison to normotensive controls 9.4 (±1.4) fL which was similar to findings detailed by Aune et al. [19].

Although preeclampsia is associated with significant increases in MPV, evidence regarding the ability of MPV to predict the disease remains conflicting. Altinbas et al.

and Dogan et al. have confirmed that preeclampsia is significantly associated with increased MPV. However, this rise in MPV did not translate to an ability to discriminate which pregnancies will ultimately develop mild versus severe preeclampsia [31, 32]. Several authors have provided a "cut-off" value of MPV as a significant predictor for preeclampsia with values ranging from 8.65 to 9.95 fL and dependant on gestational age with varying sensitivities and specificities [22, 31, 33].

In contrast to the current MPV literature, the landmark PROGNOSIS study was a prospective, multicentre, observational study, in which serum soluble-fms-like tyrosine-1: placental growth factor (s-flt-1: PlGF) ratios were measured in 1050 women with suspected preeeclampsia between 24 + 0 and 36 + 6 weeks' gestation. The authors derived and validated a serum s-flt-1:PlGF ratio of 38 that predicts lack of progression to preeclampsia in the subsequent week. In the validation arm a ratio of ≤38 had a negative predictive value of 99.3% (confidence interval 95%, 97.9–99.9) [34].

Conclusion

There is increasing evidence supporting that a diagnosis of preeclampsia results in increased platelet consumption as detailed by falling platelet counts and rising MPV. However, data from both the first trimester and postpartum remain conflicting. In this study we have not demonstrated a significant difference between first trimester MPV in EOPE when compared to uncomplicated pregnancies. As a result we are unable to recommend the use of first trimester prediction models. Given the relatively low incidence of the severe form of preeclampsia-EOPE larger multicentre trials will be necessary to provide more detailed longitudinal data and comparison with established biomarkers such as the sflt:plgf ratio to assess the clincal relevance of our reported increased MPV in the EOPE cohort.

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