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Platelet changes and subsequent development of pre-eclampsia and fetal growth restriction in women with abnormal uterine artery Doppler screening

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ABSTRACT

Objectives *To investigate whether, in women with abnormal uterine artery Doppler, platelet volume and function will identify a subgroup of women at increased risk of pre-eclampsia and intrauterine growth restriction and whether* in-vitro *platelet aggregation precedes the onset of clinical disease.*

Design *Platelet number, volume and aggregation induced by collagen or adenosine 5'-diphosphate were evaluated in 16 non-pregnant controls, 29 pregnant women with normal uterine artery Doppler and 31 pregnant women with abnormal Doppler, hence at risk of pre-eclampsia and intrauterine growth restriction at 23 weeks. Outcome of pregnancy was recorded in each case.*

Results *Twelve women in the group with abnormal uterine artery Doppler subsequently developed pre-eclampsia and/or intrauterine growth restriction. All women with normal uterine artery Doppler had a normal pregnancy outcome. No differences in platelet count or* in vitro *platelet aggregation induced by collagen were observed between the groups. Mean platelet volume was greater in those with abnormal Doppler who had intrauterine growth restriction or normal pregnancy outcome compared with normal Doppler (10.3 and 10.3 vs. 9.4 fL,* P = *0.004 and* P = *0.01, respectively). Aggregation induced by adenosine diphosphate was higher in women with abnormal Doppler who developed pre-eclampsia or intrauterine growth restriction compared with those with normal outcomes (66.5 and 66.5 vs. 21%,* P = *0.02,* P = *0.03, respectively).*

Conclusions *Women with abnormal uterine artery Doppler at 23 weeks show alterations in mean platelet volume and platelet function that relate to subsequent adverse outcome.*

INTRODUCTION

Pre-eclampsia (PE), one of the major complications of pregnancy, is characterized by increased blood pressure and proteinuria[1], and is often associated with intrauterine growth restriction (IUGR). Pre-eclampsia and/or IUGR are associated with impaired trophoblastic invasion of the maternal spiral arteries[2]. Doppler studies of the uteroplacental circulation have demonstrated that in pregnancies with impaired placentation, there is increased impedance to flow[3]. Furthermore, increased impedance to flow at 23 weeks identifies a group of patients at increased risk of subsequent development of PE and/or IUGR and especially for severe, early-onset disease[4] prior to any sign of clinical disease.

Normal pregnancy is characterized by an increase in platelet aggregation and a decrease in the number of circulating platelets with gestation[5–7]. In women with PE and/or IUGR, there is known to be a reduction in platelet count[8,9]. The changes in platelet function are more complex. Whereas in the early stages of PE platelet aggregation is increased, in established severe disease it is decreased[10]. Longitudinal studies suggest that increased platelet aggregation may predate the development of PE by 2–5 weeks[11].

The aim of this cross-sectional study was to compare changes in mean platelet volume (MPV), platelet count and function in women at 23 weeks of gestation undergoing Doppler ultrasound of the uterine arteries. Platelet changes were investigated in those with normal uterine artery Doppler and normal pregnancy outcome, and those with abnormal uterine artery Doppler who subsequently had normal or pathological (PE or IUGR) outcome.

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MATERIALS AND METHODS

All women attending for routine antenatal care at an inner city teaching hospital underwent routine uterine artery color Doppler examination at median 23 weeks' gestation (range 22–25 weeks) as part of the anomaly scan[4]. The right and left uterine arteries were identified at the apparent crossover with the external iliac artery using color Doppler. Pulsed-wave Doppler was used to obtain uterine artery waveforms using Acuson Aspen or Aloka SSD-1700 color Doppler apparatus (Acuson, Mountain View, CA, USA; Aloka, Tokyo, Japan). When three similar consecutive waveforms were obtained, the presence of an early diastolic notch was recorded, pulsatility index (PI) measured, and the mean PI of the two vessels calculated. Women with bilateral uterine artery notches, and/or those with raised impedance (mean PI of 1.45 or higher) constituted the abnormal uterine artery Doppler group[4].

The women in our study were prospectively allocated into abnormal and normal uterine artery groups. All women were healthy, normotensive and not taking any medication for at least 2 weeks prior to testing. None had a cardiovascular condition, specifically diabetes, hypertension or renal disease. All fetuses were appropriately grown for gestation and there was no ultrasound evidence of fetal anomaly.

Immediately after Doppler examination MPV, platelet count and *in vitro* platelet aggregation were examined in blood obtained from 31 women (16 primiparas, 15 multiparas) with abnormal uterine artery Doppler, 29 women (13 primiparas, 16 multiparas) with normal Doppler indices and 16 non-pregnant controls. The result of the Doppler examination was made available to the researchers performing the platelet examinations at 23 weeks. However, platelet data were concealed and only collated at the end of pregnancy.

All pregnancies were followed up for the development of PE (defined by a blood pressure of 140/90 mmHg or greater with proteinuria of at least 300 mg/24 h or dipstick testing of 300 mg/L)[1]. Fetal growth restriction (IUGR) was defined as a birth weight below the fifth centile[12]. The study was approved by the hospital ethics committee, and informed consent was obtained from the patients and non-pregnant controls.

Twenty milliliters of blood was obtained by anticubital venepuncture without stasis and collected into a polypropylene vial containing 3.15% sodium citrate solution (v:v, 9 : 1). The platelet count and MPV in whole blood were measured immediately using a Coulter Counter (Sysmex Ltd, Buckinghamshire, UK). *In vitro* platelet aggregation studies were performed using platelet-rich plasma (PRP) according to the method of Born[13]. Blood was centrifuged at 200 *g* for 20 min within 15 min after collection and PRP was aspirated. The remainder of the sample was centrifuged at 600 *g* for 10 min to obtain platelet-poor plasma (PPP). Platelet count in PRPs was adjusted to 2–2.5 $\times 10^{11}$/L using autologous PPP and the PRP kept still at room temperature for 30 min. *In vitro* platelet aggregation was monitored using a dual-channel Chrono-Log-aggregometer (Chrono-Log Corporation, Havertown, PA, USA) at 37°C with continuous stirring. The aggregometer was connected to a computer database, and the data analyzed using Aggro/Link software (Chrono-Log Corporation). Collagen (Horm, Nycomed Arzneimittel, Munich, Germany) and adenosine 5′-diphosphate (ADP, Sigma-Aldrich, Poole, UK) in increasing concentrations (0.5, 1, 2, 4 μg/mL) and (0.5, 1, 2, 5 μM), respectively, were used as pro-aggregating agents. *In vitro* platelet aggregation was monitored for 6 min after addition of the respective concentration of the pro-aggregating agents. *In vitro* platelet aggregation was expressed as a percentage of the light transmission at 6 min related to the negative control (PPP).

Statistical analysis

Comparisons were made between MPV, platelet count and *in vitro* platelet aggregation in women screened by uterine artery Doppler with normal and abnormal uterine artery Doppler, and non-pregnant controls. Further comparisons between MPV, platelet count and *in vitro* platelet aggregation in women with normal uterine artery Doppler were made with those with abnormal uterine artery Doppler according to pregnancy outcome (PE or IUGR). In all cases the non-parametric Mann–Whitney *U*-test was used to investigate the differences between the groups using STATA version 6.0 (STATA Corporation, College Station, TX, USA).

RESULTS

The presence of abnormal uterine artery Doppler in the local population of our inner city teaching hospital was about 6%[4]. The characteristics of the normal and abnormal uterine artery Doppler groups are described in Table 1. The study and the control groups were drawn from over 1000 women undergoing uterine artery Doppler screening over a 1-year period after individual consent. All 29 pregnancies with normal uterine artery Doppler at 22–25 weeks had a normal pregnancy outcome. In the 31 women with abnormal uterine artery Doppler at 23 weeks, eight developed PE 5–15 (median, 12) weeks after screening, of whom four also developed IUGR. Four women delivered babies with IUGR at 36–40 (median, 40) weeks' gestation without PE. Two women had a placental abruption of which one resulted in an

Table 1 Demographics and outcome of women with normal and abnormal uterine artery Doppler at 23 weeks.

	Normal uterine artery Doppler (n = *29*)	*Abnormal uterine artery Doppler* (n = *31*)
Parity (*n* (%))		
Primipara	13 (44.8)	16 (51.6)
Multipara	16 (55.2)	15 (48.4)
Ethnicity (*n* (%))		
Afro-Caribbean	6 (20.7)	17 (54.8)
Caucasian	18 (62)	11 (35.5)
Other	5 (17.3)	3 (9.7)
GA at delivery (days, mean (SD))	278 (13)	268 (23)
Birth weight (g, mean (SD))	3425 (609)	2616 (728)

SD, standard deviation; GA, gestational age.

Table 2 Mean platelet volume, platelet count and function in non-pregnant women and in women with normal and abnormal uterine artery Doppler at 23 weeks

	Median	*Interquartile range*
Platelet count ($\times 10^9$/L)		
Non-pregnant	198	181–231
Normal Doppler	184	167–199
Abnormal Doppler	167	133–229
Mean platelet volume (fL)		
Non-pregnant	9.25	8.65–9.6
Normal Doppler	9.4	9.2–9.6
Abnormal Doppler	10.2*	9.1–10.9
Platelet aggregation with collagen (%)		
Non-pregnant	61	26–66
Normal Doppler	65	56–72
Abnormal Doppler	70	60–73
Platelet aggregation with ADP (%)		
Non-pregnant	13	7.5–26
Normal Doppler	37†	14–71
Abnormal Doppler	40‡	12–70

Non-pregnant $n = 16$; normal Doppler $n = 29$; abnormal Doppler $n = 31$.
*$P = 0.02$ compared with normal uterine artery Doppler.
†$P = 0.02$ compared to non-pregnant controls, ‡$P = 0.03$ compared with non-pregnant controls.

intrauterine death. The remaining 17 pregnancies were not complicated by adverse outcome.

Mean platelet volume, platelet count and platelet function in non-pregnant controls and the pregnant women with normal and abnormal uterine artery Doppler at 23 weeks are shown in Table 2 and Figure 1 and values in relation to pregnancy outcome are shown in Table 3 and Figure 2. When all the data were pooled there was a significant correlation between MPV and platelet count ($r = -0.553$, $P < 0.0001$). Two women with abnormal Doppler subsequently had placental abruption but as these were not associated with PE or IUGR we included their data in the screening statistics, but excluded them from the outcome analysis as no outcome group adequately described their pathology.

No significant differences in platelet count and *in vitro* platelet aggregation induced by collagen were seen between pregnant women with normal and abnormal uterine artery Doppler, and non-pregnant controls. Differences in MPV and *in vitro* platelet aggregation using ADP 1 μM as pro-aggregating agents were observed between the groups. This concentration of ADP was used as it identified the greatest separation between the groups; similar results were observed with 0.5 μM, whereas 2 μM resulted in near maximal aggregation.

Mean platelet volume was greater in women with abnormal uterine artery Doppler compared with those with normal Doppler (10.2 vs. 9.4 fL, $P = 0.02$) (Table 2 and Figure 1).

In vitro platelet aggregation by ADP was increased in pregnant women with normal and abnormal uterine artery Doppler compared with non-pregnant controls (37 vs. 13%, $P = 0.02$ and 40 vs. 13%, $P = 0.03$) (Table 2 and Figure 1).

Mean platelet volume was significantly higher (10.3 vs. 9.4 fL, $P = 0.01$) in the women with abnormal uterine artery

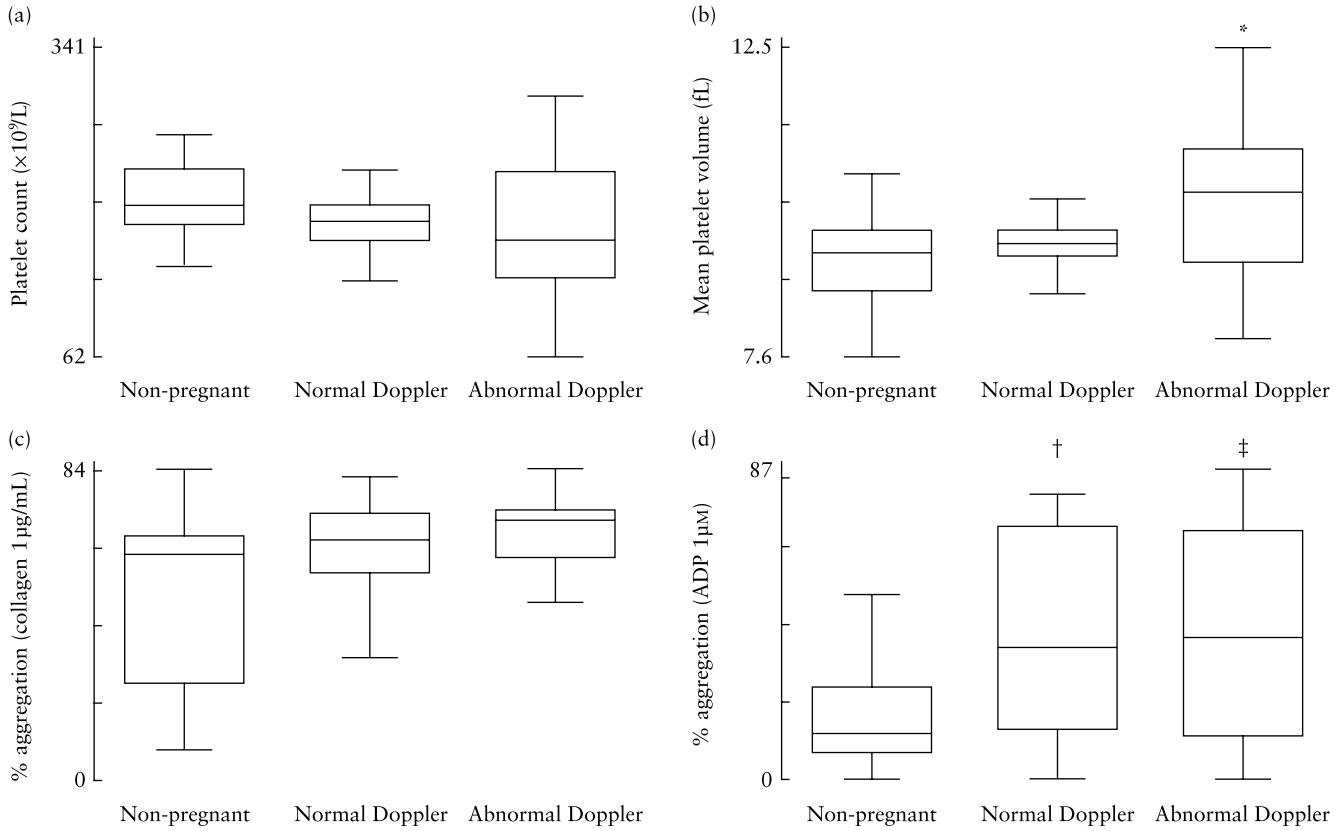

Figure 1 Box and whisker plots of platelet count (a), mean platelet volume (MPV) (b), *in vitro* platelet aggregation induced by 1 μg/mL collagen (c) and *in vitro* platelet aggregation induced by 1 μM ADP (d) in non-pregnant women and women with normal and abnormal uterine artery Doppler at 23 weeks. Non-pregnant women $n = 16$, normal Doppler $n = 29$, abnormal Doppler $n = 31$. *$P = 0.02$ compared with normal uterine artery Doppler. †$P = 0.02$ compared with non-pregnant controls, ‡$P = 0.03$ compared with non-pregnant controls.

Table 3 Mean platelet volume, platelet count and function in women with normal and abnormal uterine artery Doppler classified according to outcome

	Median	*Range*
Platelet count ($\times 10^9$/L)		
Normal Doppler	184	145–341
Abnormal Doppler, normal outcome	144	62–235
Abnormal Doppler, pre-eclampsia	202	149–296
Abnormal Doppler, IUGR	165	99–226
Mean platelet volume (fL)		
Normal Doppler	9.4	8.1–10.7
Abnormal Doppler, normal outcome	10.3*	8.6–12.5
Abnormal Doppler, pre-eclampsia	9.1	8.3–11
Abnormal Doppler, IUGR	10.3†	9.8–12.2
Platelet aggregation with collagen (%)		
Normal Doppler	65	13–82
Abnormal Doppler, normal outcome	66	0–83
Abnormal Doppler, pre-eclampsia	72	60–84
Abnormal Doppler, IUGR	66.5	51–70
Platelet aggregation with ADP (%)		
Normal Doppler	37	0–80
Abnormal Doppler, normal outcome	21	0–77
Abnormal Doppler, pre-eclampsia	66.5‡	12–79
Abnormal Doppler, IUGR	66.5§	37–87

IUGR, intrauterine growth restriction. Normal Doppler $n = 29$; abnormal Doppler, normal outcome $n = 17$; abnormal Doppler, pre-eclampsia $n = 8$; abnormal Doppler, IUGR $n = 4$.
*$P = 0.01$ compared with normal uterine artery Doppler, †$P = 0.004$ compared with normal uterine artery Doppler. ‡$P = 0.02$ compared with abnormal uterine artery Doppler/normal outcome, §$P = 0.03$ compared with abnormal uterine artery Doppler/normal outcome.

Doppler but normal pregnancy outcome, compared with those with normal Doppler (Table 3 and Figure 2). *In vitro* platelet aggregation with ADP was lower in those with abnormal uterine artery Doppler and normal pregnancy outcome compared with women with normal uterine artery Doppler, but this was of borderline significance (21 vs. 37%, $P = 0.08$).

Eight women with abnormal uterine artery Doppler who subsequently developed PE had similar platelet number, volume and aggregation to both collagen and ADP, whether or not IUGR was present (four in each group). We considered these women as pre-eclamptic.

In the group with abnormal uterine artery Doppler, the women who developed PE had normal MPV but significantly higher ADP-induced *in vitro* platelet aggregation than those with normal outcome (66.5 vs. 21%, $P = 0.02$).

In women with abnormal uterine artery Doppler who delivered IUGR infants compared with those with abnormal Doppler but normally grown infants, MPV did not differ but ADP-induced *in vitro* platelet aggregation was higher (66.5 vs. 21%, $P = 0.03$) (Figure 2 and Table 3).

We observed the highest MPV in women with abnormal uterine artery blood flow and either normally grown or IUGR infants. ADP-induced *in vitro* platelet aggregation was highest in those with abnormal uterine artery Doppler and subsequent development of PE and/or IUGR (Table 3 and Figure 2).

DISCUSSION

In agreement with a previous study[5], we were unable to demonstrate a significant change in platelet count and MPV at 23 weeks' gestation in normal pregnancy compared with non-pregnant controls. However, we did observe a significant increase in platelet aggregation induced by ADP. As found in our previous study, MPV in women with abnormal uterine artery Doppler was increased in comparison with women with normal uterine artery Doppler[14]. The difference in the absolute measured MPV between the studies is most likely related to the different method used by Lees *et al.*[14], as they centrifuged the blood at 190 *g* for 20 min and measured MPV in PRP, which is known to affect their MPVs[15]. In this study, the data suggest that in women with abnormal uterine artery Doppler, MPV and platelet function are altered with specific patterns of change associated with subsequent adverse pregnancy outcome. Impaired placentation and increased impedance to flow may cause endothelial changes due to increased shear stress or alterations in circulating platelets[16,17].

We used two pro-aggregating reagents to assess *in vitro* platelet function and demonstrated differences in the response of platelets in the various subgroups to these reagents. Collagen causes direct mechanical rupture and aggregation of the platelets, and no significant difference could be observed between the normal and abnormal groups with maximum *in vitro* aggregation achieved in both. Using ADP, the *in vitro* aggregation in the normal outcome groups was about 30%, whereas in those that subsequently developed PE or IUGR, aggregation was twice as high. Because the effects of ADP on platelets are membrane-receptor-mediated[18], our results suggest changes in the membrane receptors and/or changes in the intracellular response of platelets in women with abnormal pregnancy outcome.

In the group with abnormal Doppler, those that subsequently developed IUGR had increased MPV and ADP-induced *in vitro* platelet aggregation. In this group there may be increased consumption of platelets in the uteroplacental circulation leading to a reduction in the number of circulating platelets, and a compensatory increase in bone marrow platelet production. Platelet consumption results in the physiological release of younger platelets which are known to have a higher MPV and aggregation tendency[19,20]. It has been suggested that platelet consumption might be confined to the uteroplacental circulation causing IUGR but no other pathological maternal sequelae[21]. In contrast, in the group with abnormal Doppler but normal fetal growth, MPV was increased but ADP-induced *in vitro* platelet aggregation was normal. In this group platelet consumption and destruction may occur systemically rather than in the uteroplacental circulation, hence are not associated with increased aggregation and are not leading to significant uteroplacental insufficiency and IUGR.

In the group with abnormal uterine artery Doppler that subsequently developed PE, there was normal platelet count and MPV but increased ADP-induced *in vitro* platelet aggregation. This alteration in platelet function may be an early response predating changes in MPV which have been shown to increase 2–5 weeks before the onset of clinical disease[11,22].

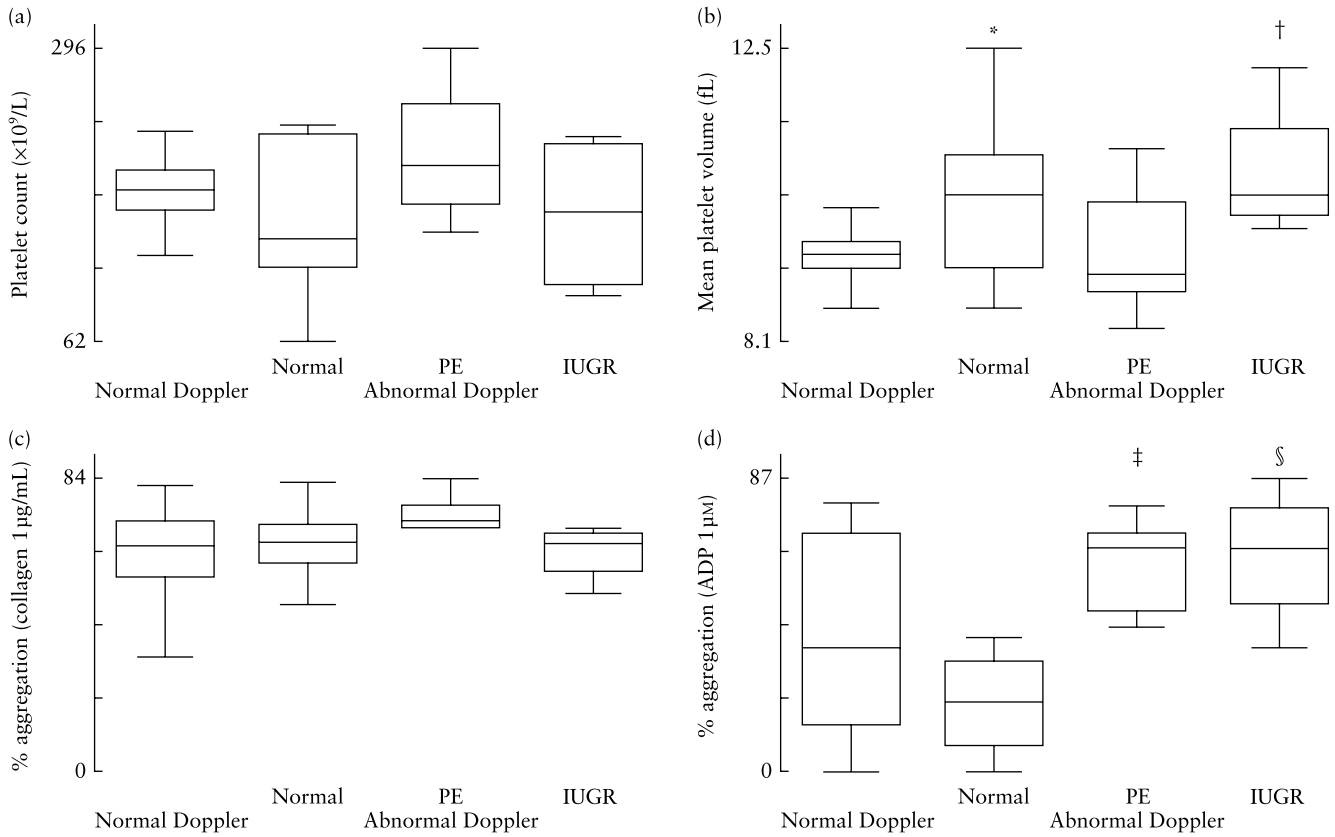

Figure 2 Box and whisker plots of platelet count (a), mean platelet volume (MPV) (b), *in vitro* platelet aggregation induced by 1 μg/mL collagen (c) and *in vitro* platelet aggregation induced by 1 μM ADP (d) in women with normal and abnormal uterine artery Doppler classified according to pregnancy outcome. Normal Doppler $n = 29$, abnormal Doppler, normal outcome $n = 17$, abnormal Doppler, pre-eclampsia $n = 8$, abnormal Doppler, IUGR $n = 4$. *$P = 0.01$ compared with normal uterine artery Doppler, †$P = 0.004$ compared with normal uterine artery Doppler. ‡$P = 0.02$ compared with abnormal uterine artery Doppler/normal outcome, §$P = 0.03$ compared with abnormal uterine artery Doppler/normal outcome. IUGR, intrauterine growth restriction; PE, pre-eclampsia.

These subtle changes may later lead to sudden onset of clinical disease with progressive platelet consumption. The observed change in platelet function without a change in platelet volume and count at 23 weeks is consistent with the suggestion of Roberts and Redman[23] that in PE there is/are (a) factor(s) in the maternal circulation which may affect the endothelium and circulating platelets predating changes in platelet morphology.

This study demonstrates changes in MPV and platelet function in women with abnormal Doppler who later developed PE and/or IUGR. Although the numbers of women in the abnormal Doppler/PE and abnormal Doppler/IUGR groups are small (eight and four, respectively) the differences observed in MPV and ADP-induced *in vitro* platelet aggregation are significant using non-parametric tests.

Both PE and IUGR are characterized by impaired trophoblast invasion of the maternal spiral arteries, but the pattern of changes in platelet morphology and function may be disease-specific. These tests are too labor-intensive, expensive and not sufficiently specific to be applicable to clinical screening or risk assessment. However, the changes in platelet function and MPV described in this study imply that the pattern of subsequent pathology (IUGR or PE) resulting from impaired placentation is demonstrable many weeks before the clinical onset of the disease, and may relate to the specific pathophysiology of each condition.

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