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Platelet aggregation and thromboelastometry monitoring in women with preeclampsia: A prospective observational study.

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Abstract

Background

Thrombocytopenia affects 12-20% of women with preeclampsia and a low platelet count impairs coagulation. Women with preeclampsia have an increased risk of both cerebral hemorrhage, thromboembolism, and postpartum hemorrhage. Studies of platelet function and coagulation in women with preeclampsia show conflicting results. Therefore, we aimed to study platelet aggregation and coagulation in women with preeclampsia.

Method

Women with preeclampsia and women with normotensive pregnancies were included prior to delivery in a prospective observational study as a part of the Gothenburg Preeclampsia Adverse Event (GoPROVE) Biobank and Database. Sampling and analyses were performed shortly before delivery. Platelet count was analyzed and impedance aggregometry was used for examining platelet adhesion and aggregation. Thromboelastometry was used to assess coagulation.

Results

Ninety-three women with preeclampsia and 45 normotensive pregnant control patients were included. There was no difference in platelet aggregation (adenosine diphosphate, ADP-test), (arachidonic acid, ASPI-test) or (thrombin receptor-activating peptide, TRAP-test) between women with preeclampsia and women with normotensive pregnancies. Women with preeclampsia had lower platelet counts, shorter clotting (EXTEM-CT and INTEM-CT) and clot formation (EXTEM-CFT and INTEM-CFT) times than women with normotensive pregnancies. Platelet aggregation and coagulation were hyperactivated in women with preeclampsia and normal platelet counts. In women with preeclampsia and thrombocytopenia, platelet aggregation and thromboelastic tests of coagulation were impaired compared to normotensive pregnancies.

Conclusion

Platelet aggregation and thromboelastic tests of coagulation are dependent on platelet counts in women with preeclampsia. At normal platelet counts, women with preeclampsia have a hyperactivated tests of coagulation. In contrast, women with thrombocytopenia demonstrated lower coagulation test values.

Keywords: Coagulation, Monitoring, , Platelet aggregation, Preeclampsia, Thrombocytopenia, Thromboelastometry

Introduction

Preeclampsia complicates 3–5% of all pregnancies and represents a leading cause of maternal and neonatal morbidity and mortality worldwide.[1,2] The central theory is that preeclampsia is triggered by the release of vasoactive substances from the uteroplacental unit that contributes to subsequent widespread maternal endothelial dysfunction.[1,2] Coagulation disturbances are common in women with preeclampsia.[3] Women with preeclampsia also have an increased risk of both bleeding and thromboses, including cerebral hemorrhage, thromboembolism, and postpartum hemorrhage.[4-8]

For women with preeclampsia, spinal anesthesia is preferred during caesarean delivery to avoid the risks of cerebral hemorrhage during tracheal intubation. However, some women with preeclampsia may have an increased risk of spinal hematoma due to low platelet count.[9,10,11] These risks are challenging to balance. Thrombocytopenia is common, affecting 12-20% of women with preeclampsia, and coagulation is hyperactivated due to endothelial injury.[1-3,5,8]

Platelets affect both primary and secondary hemostasis by forming and maintaining blood clots. Platelet count is considered important. Based on international consensus, a platelet count greater than 70 x 10^9/L is usually considered sufficient, after clinical assessment, for safe spinal anesthesia.[9-11] However, new methods for the surveillance of coagulation integrated into clinical practice in trauma and major surgery are becoming more commonly used in obstetric care.[12-15] Impedance aggregometry (Multiplate®) is used to monitor adhesion and aggregation of platelets and thromboelastometry (ROTEM®) to assess coagulation function. The role of platelet aggregation in preeclampsia, and how a declining platelet count affects platelet aggregation and coagulation, have not been extensively studied; and currently published study result are conflicting.[14-18]

Our hypothesis is that preeclampsia changes platelet aggregation and coagulation compared to normotensive pregnancies and the differences are associated with the platelet concentration in women with preeclampsia. Therefore, our primary aim was to investigate platelet aggregation and coagulation in women with preeclampsia compared to normotensive pregnancies regardless of platelet count. Secondly, we examined how platelet aggregation and coagulation were affected at different platelet counts in preeclampsia. Finally, we examined platelet aggregation and coagulation in women with preeclampsia with and without severe features and complications.

Method

Population

Women with preeclampsia were included at diagnosis and women with normotensive pregnancies were included at first hospital visit in a prospective observational study as a part of the Gothenburg Preeclampsia Adverse Event (GoPROVE) Biobank and Database.[19] The study design and all measurements were planned before recruitment of patients to the present study. Women were enrolled by staff, PhD students and research assistants at Sahlgrenska University Hospital, a tertiary university hospital with approximately 11,000 births annually. All women with a diagnosis of preeclampsia were eligible for inclusion. Women with multifetal pregnancies, prior diagnosis of chronic hypertension, or any significant systemic disease such as diabetes were not included in this study. The study was approved by the Regional Research Committee in Gothenburg (registration number EPM 955-18, 2019-03734, 2020-02291) Enrollment in the present study occurred between October 2019 and February

2022. The biometrics and standard laboratory results of the women were retrieved from the GoPROVE database, an electronic case report form with double authentication provided by MedSciNet®.[19] ROTEM® and Multiplate® were performed on blood samples exclusively on the women included in this study, not on all women included in GoPROVE (Figure 1).

Exposures

Preeclampsia and severe features of preeclampsia were defined according to the criteria of the American College of Obstetricians and Gynecologists, with the additional criterium that only women with elevated proteinuria (albumin/creatinine ratio >8 mg/mmol) were included.[20] Small-for-gestational age (SGA) was defined as -2 standard deviations for gestational age according to Swedish reference curves.[21] Severe thrombocytopenia was defined as platelet count <100 x 10^9/L, mild thrombocytopenia was defined as platelet count between 100-150 x 10^9/L, and normal platelet count was defined as platelet count >150 x 10^9/L. All variables from the medical records were inserted into the GoProve database and were double checked for accuracy.

Outcomes

Impedance Aggregometry (Multiplate®) was used to assess platelet adhesion and aggregation and coagulation was assessed with thromboelastometry (ROTEM®). Analyses were performed as close as possible to the time of delivery (within 24 hours).

*Sample collection:i*ROTEM® and MULTIPLATE® were managed according to routine clinical practice and analyzed within recommended time interval after sampling, at the Pediatric Intensive Care Unit and the Obstetric Surgery ward at Sahlgrenska University Hospital.

Whole blood was sampled through a fresh venipuncture (18-G needle) directly into three different vacuum test tubes for the analyses. For platelet count, in K2-EDTA 5-mL test tubes, for platelet adhesion and aggregation in heparin-anticoagulated Vacate LH Lithium Heparin test tubes (Greiner Bio-One GmbH), and for coagulation measured with ROTEM®, a citrate-containing test tube (Greiner Bio-One) was used.

Sample analyses

Platelet count was analyzed with the Advia 2120i® (Siemens Healthineers, Erlingen, Germany), the standard method used by the accredited Sahlgrenska University Hospital laboratory. This method uses flowcytometry and phase contrast microscopy to count platelets.

Platelet adhesion and aggregation were analyzed using impedance aggregometry (Multiplate® Roche Diagnostics, Switzerland). The test kits used were as follows: adenosine diphosphate (ADP-test) for the detection of P2Y12-dependent aggregation, the arachidonic acid (ASPI-test) to assess cyclooxygenase-dependent platelet aggregation, and the thrombin receptor-activating peptide (TRAP) test to assess PAR-1 receptor-dependent platelet aggregation. The change in impedance in the test is expressed as the area under the curve, as a quantification of platelet aggregation, reported in arbitrary aggregation units (U). Coagulation was analyzed by rotational thromboelastometry (ROTEM®; Pentapharm GmbH). Clotting time (CT), clot formation time (CFT), maximum clot firmness (MCF) in the EXTEM, INTEM and FIBTEM channels were analyzed. The technical details of Multiplate® and ROTEM® and evaluation of the methods have been reported previously. [22,23] (supplemental data 1).

Statistical analysis

Continuous data were presented as median (interquartile range). For the comparison of continuous variables between two groups, the Mann Whitney U test was used. The Jonckhere-

Terpstra test for trends among groups was used to compare the aggregation and thromboelastrography tests among the women with preeclampsia with normal platelet count, and mild and severe thrombocytopenia. Fishers exact test was used to compare binary outcomes between two groups and the chi-squared test was used to compare outcomes of nominal data with more than two variables in any group. A *P* value <0.05 was considered statistically significant. Statistical analyses were carried out with the SPSS software version 25.0 (Armonk, NY, USA).

The study was a prospective observational study; there were limited data on platelet aggregation in women with preeclampsia. A sample size estimation was performed: we assumed a 20% standard deviation in platelet aggregation data and anticipated a 10% decrease in platelet aggregation values in the preeclampsia group. With a 2:1 enrollment ratio, this result in a sample size of 94 women in the preeclampsia group and 47 women in the control group.

Results

A total of 95 women with preeclampsia were included in the study. Two women were excluded from analysis, one due to active protein C resistance and another due to prothrombin gene mutation, resulting in 93 women in the final analysis. In total, 50 women with normotensive pregnancies were enrolled. Three were excluded due to development of preeclampsia after inclusion and two were excluded due to incomplete tests, resulting in 45 women in the control group (Fig 1). There was one intrauterine fetal death reported among the women with preeclampsia. Baseline characteristics on the included patients are described in Table 1. The women with preeclampsia had higher body mass index, were more commonly nulliparous, and were of lower gestational age than the control patients.

Women with preeclampsia had a lower platelet count than women with normotensive pregnancies (Table 2). There were no differences in platelet aggregation adenosine diphosphate (ADP), arachidonic acid (ASPI), or thrombin receptor-activating peptide (TRAP) between the two groups. Women with preeclampsia had shorter coagulation times (EXTEM-CT) and shorter clot formation times (EXTEM-CFT).

Seven of the women with preeclampsia using prophylactic aspirin therapy (75 mg, last dose within 7 days) had no significant difference on the ASPI-test compared to normotensive women.

Sixty-three women with preeclampsia had a normal platelet count, 23 had mild thrombocytopenia and seven women had severe thrombocytopenia. Women with preeclampsia and normal platelet count had shorter INTEM-CFT and EXTEM-CFT times and higher INTEM-MCF and EXTEM-MCF values compared to normotensive pregnancies. Women with preeclampsia and mild thrombocytopenia had less platelet aggregation measured as lower counts of ADP and ASPI units compared to normotensive pregnancies. They also had shorter EXTEM-CT time and lower INTEM-MCF and EXTEM-MCF values. Women with preeclampsia and severe thrombocytopenia had longer INTEM-CFT and EXTEM-CFT and lower INTEM-MCF and EXTEM-MCF compared to normotensive pregnancies.

The Jonckhere-Terpstra test showed a statistical significance for lower ADP counts and lower INTEM-MCF and EXTEM-MCF, as well as longer clotting time in INTEM-CT and longer clot formation times in EXTEM-CFT and INTEM-CFT when platelet count decreased within the group of women with preeclampsia (Fig. 2).

There were no differences in platelet aggregation and coagulation in women with preeclampsia with one or more severe features compared to women with preeclampsia without severe features (Table 3). In a subgroup analysis, the only complication of preeclampsia associated with altered coagulation was found in women with small-for-gestational-age neonates; these women had increased platelet aggregation (higher TRAP-counts) (Supplemental Material 2).

Discussion

Platelet aggregation and thromboelastic tests of coagulation are dependent on platelet counts in women with preeclampsia. At normal platelet counts, women with preeclampsia have a hyperactivated tests of coagulation. In contrast, women with thrombocytopenia demonstrated lower coagulation test values.

We found no difference in platelet aggregation (ADP, ASPI, or TRAP-test) between women with preeclampsia and normotensive women, probably due to the heterogeneity of platelet counts in the group of women with preeclampsia. Women with preeclampsia had a faster onset of coagulation compared to women with normotensive pregnancies. This is consistent with previous research in which Spezia et al. also found a faster onset of coagulation measured with thromboelastography (TEG®) in women with preeclampsia compared to women with normotensive pregnancies.[16] Another study reported that women with preeclampsia who had normal platelet counts had faster onset of coagulation, more stable clots, and no difference in aggregation compared to women with normotensive pregnancies.[24] Davis et al. showed that the platelet aggregation measured with PFA-100 detected impaired platelet aggregation in women with preeclampsia while thromboelastography (TEG) did not detect coagulopathy.[17]

We also examined how platelet aggregation and coagulation were affected at different platelet counts in preeclampsia. At normal platelet counts, women with preeclampsia had a faster onset of clotting and stronger clot formation than normotensive women. When preeclampsia was complicated by thrombocytopenia, even mild thrombocytopenia, a decline in platelet aggregation was observed. Maximum clot firmness was also slightly decreased while the clotting time was faster. Our study indicates that, in women with preeclampsia, a platelet count $< 150 \times 10^9$/L is associated with altered tests of coagulation.

Despite a small number of women with severe thrombocytopenia, we found a decrease in clot formation time (EX-CFT, IN-CFT) and the maximum clot firmness (EX-MCF, IN-MCF). Leduc et al. found similar results, with a general decrease in activated partial thromboplastin time (aPTT) and prothrombin time (PT) when the platelet count declined to less than 100×10^9/L.[24] Consistent with our study, the Roadmap -Preeclampsia study found slower onset of clot formation and decreased maximum clot firmness in women with severe preeclampsia (one criterium for severe preeclampsia is thrombocytopenia).[18]

A consensus statement from the Society for Obstetric Anesthesia and Perinatology discussed neuraxial procedures and the risk for spinal hematoma in patients with thrombocytopenia. The

experts agreed that, regardless of pathogenesis of thrombocytopenia, a platelet level greater than 70 x10^9/L is sufficient for the safe use of spinal anesthesia after clinical assessment.[10]

The ADP receptors, crucial to metabolism, have been suggested by others to play a role in the development of preeclampsia.[25] Clopidogrel is being investigated as a possible treatment of preeclampsia because of the effect on antioxidant defense and suppressed endothelial dysfunction.[26]

Women with preeclampsia and small-for-gestational-age (SGA) neonates had increased aggregation, but unaltered coagulation compared to women with preeclampsia without SGA. Norris et al. suggested that the release of vasoactive amines from activated platelets in the peripheral circulation may be responsible for the clinical syndrome of hypertension and proteinuria present in pregnancies complicated by preeclampsia and fetal growth restriction (FGR); this is absent in normotensive women with FGR.[27] One possible explanation for the association between increased platelet aggregation and SGA is that elevated platelet aggregation may cause microthrombi and infarctions in the placenta, a common histopathological finding in preeclampsia.[28] This outcome might in turn contribute to an impaired placental function and subsequent impaired fetal growth.[28]

Platelet aggregation (Multiplate®) and coagulation (ROTEM®) measurements can be used bedside and can provide additional information about platelet aggregation and coagulation in preeclampsia. Observation of platelet function and its relation to platelet count might provide new insights into preeclampsia pathophysiology. We suggest further studies to confirm our results and evaluate if platelet count is enough for developing safe strategies for clinical decisions such as spinal or general anesthesia or for assessing risk for thromboembolism. Clinical recommendations cannot be undertaken based on this single study. Future studies should assess platelet function in a larger cohort of women with preeclampsia and severe thrombocytopenia.

Strengths of this study included well-characterized women with preeclampsia and normotensive controls enrolled prospectively in a large university hospital setting. The analyses of coagulation and platelet function were assessed using validated instruments. The study also has some limitations. Only 7 women had severe thrombocytopenia. This small number might be due to the difficulty of enrolling women with severe thrombocytopenia for analyses of coagulation function before delivery. These women are often delivered within a few hours of presenting to the hospital, and are thus challenging to include in a prospective study. Another limitation is the platelet aggregation method (Multiplate®) which has an inter-individual variance that might influence results and clinical interpretations.[29]

Conclusion

Platelet aggregation and thromboelastic tests of coagulation are dependent on platelet counts in women with preeclampsia. At normal platelet counts, women with preeclampsia have a hyperactivated tests of coagulation. In contrast, women with thrombocytopenia demonstrated lower coagulation test values.

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Declaration of interests

The authors declare no conflicts of interest.

Authors contributions

All authors contributed to key elements of the study design and data acquisition. All authors reviewed the manuscript and approved the definitive version.

References

1. Chappell, Lucy C *et al*. Pre-eclampsia. *The Lancet*, 2021;Volume 398:341–354 . https:// doi: 10.1016/S0140-6736(20)32335-7.

2. Magee LA, Brown MA, Hall DR, *et al*. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens.* 2022 Mar; 27:148-169. doi: 10.1016/j.preghy.2021.09.008. Epub 2021 Oct 9. PMID: 35066406.

3. Peng J, Zhao Q, Pang W, *et al*. Changes of coagulation function and platelet parameters in preeclampsia and their correlation with pregnancy outcomes. *J Clin Hypertens* (Greenwich). 2024 Aug 26. doi: 10.1111/jch.14893. Epub ahead of print. PMID: 39185609.

4. Raia-Barjat T, Edebiri O, Ni Ainle F, *et al*. Preeclampsia and Venous Thromboembolism: Pathophysiology and Potential Therapy. *Front Cardiovasc Med*. 2022;9:856923. https://doi: 10.3389/fcvm.2022.856923.

5. Jakobsen C, Brogaard, Larsen J*, et al.* Platelet function in preeclampsia – a systematic review and meta-analysis*. Platelets.* 2019;30:549-562. https://doi: 10.1080/09537104.2019.1595561

6. Scheres LJJ, Lijfering WM, Groenewegen NFM*, et al*. Hypertensive Complications of Pregnancy and Risk of Venous Thromboembolism. *Hypertension*. 2020;75:781-787. https:// doi: 10.1161/HYPERTENSIONAHA.119.14280.

7. von Schmidt auf Altenstadt JF, Hukkelhoven CW, van Roosmalen J, *et al*. Pre-eclampsia increases the risk of postpartum haemorrhage: a nationwide cohort study in the Netherlands. *PLoS One*.2013;8:e81959. https://doi.org/10.1371/journal.pone.0081959

8. ACOG Practice Bulletin No. 207: Thrombocytopenia in Pregnancy. *Obstet Gynecol.* 2019;133:e181-e93. https://doi: 10.1097/AOG.0000000000003100. PMID: 30801473

9. Breivik H, Bang U, Jalonen J, *et al*. Nordic guidelines for neuraxial blocks in disturbed haemostasis from the Scandinavian Society of Anaesthesiology and Intensive Care Medicine. *Acta Anaesthesiol Scand*. 2010;54:16-41. https://doi: 10.1111/j.1399-6576.2009.02089.x

10. Bauer ME, Arendt K, Beilin Y, *et al*. The Society for Obstetric Anesthesia and Perinatology Interdisciplinary Consensus Statement on Neuraxial Procedures in Obstetric Patients With Thrombocytopenia. *Anesth Analg*. 2021;132:1531-1544. https://doi:10.1213/ANE.0000000000005355

11. Regional anaesthesia and patients with abnormalities of coagulation.The Association of Anaesthetists of Great Britain & Ireland. The Obstetric Anaesthetists' Association Regional Anaesthesia UK. *Anaesthesia*. 2013:966-972. https://doi.org/10.1111/anae.12359

12. Weber CF, Gorlinger K, Meininger D*, et al*. Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. *Anesthesiology.* 2012;117:531-547. https://doi: 10.1097/ALN.0b013e318264c644

13. Reinhöfer M, Brauer M, Franke U*, et al.* The value of rotation thromboelastometry to monitor disturbed perioperative haemostasis and bleeding risk in patients with cardiopulmonary bypass. *Blood coagulation & fibrinolysis* : *an international journal in haemostasis and thrombosis.* 2008;19:212-219. https://doi: 10.1097/MBC.0b013e3282f3f9d4

14. Armstrong S, Fernando R, Ashpole K*, et al*. Assessment of coagulation in the obstetric population using ROTEM(R) thromboelastometry. *Int J Obstet Anesth*. 2011;20:293-298. https://doi: 10.1016/j.ijoa.2011.05.004

15. Sharma Shiv K, Philip J, Whitten Charles W*, et al*. Assessment of Changes in Coagulation in Parturients with Preeclampsia Using Thromboelastography. *Anesthesiology*. 1999;90:385-390. https://doi: 10.1097/00000542-199902000-00009

16. Spiezia L, Bogana G, Campello E, *et al*. Whole blood thromboelastometry profiles in women with preeclampsia*. Clinical chemistry and laboratory medicine*. 2015;53:1793-1798. https://doi: 10.1515/cclm-2014-1128

17. Davies JR, Fernando R, Hallworth SP, *et al*. Hemostatic function in healthy pregnant and preeclamptic women: an assessment using the platelet function analyzer (PFA-100) and thromboelastograph. *Anesth Analg*. 2007;104:416-420.https://doi:10.1213/01.ane.0000253510.00213.05

18. Van Dreeden P, Lefkou E, Ka A**,** *et al*. Profile of Thrombin Generation Assay and Thromboelastometry in Women with Moderate and Severe Preeclampsia. The ROADMAP-EOP Study. *Clin Appl Thromb Hemost.* 2022;28:10760296221138296. https://doi:10.1177/10760296221138296

19. Thorgeirsdottir L, Andersson M, Karlsson O, *et al*. Study protocol: establishment of a multicentre pre-eclampsia database and biobank in Sweden: GO PROVE and UP MOST, a prospective cohort study**.** *BMJ Open*. 2021;11:e049559. https://doi: 10.1136/bmjopen-2021-049559

20. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. *Obstet Gynecol*. 2020;135:e237-e60. https:// doi: 10.1097/AOG.0000000000003891

21. Marsál K, Persson PH, Larsen T, *et al*. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr*. 1996;85:843-848. https:// doi: 10.1111/j.1651-2227.1996.tb14164.x

22. Würtz M, Hvas AM, Christensen KH *et al*. Rapid evaluation of platelet function using the Multiplate® Analyzer. *Platelets.* 2014;25:628-633. doi: 10.3109/09537104.2013.849804. Epub 2013 Nov 18. PMID: 24246241.

23. Luddington RJ. Thrombelastography/thromboelastometry. *Clinical and laboratory haematology*. 2005;27:81-90. https://doi: 10.1111/j.1365-2257.2005.00681.x

24. Leduc L, Wheeler JM, Kirshon B, *et al*. Coagulation profile in severe preeclampsia. *Obstet Gynecol*. 1992;79:14-18. PMID: 1727573.

25. Wihlborg AK, Wang L, Braun OO, *et al*. ADP-receptor P2Y12 is expressed in vascular smooth muscle cells and stimulates contraction in human blood vessels. *Arterioscler Thromb Vasc Biol*. 2004; 24:1810-1815. https://doi:10.1161/01.ATV.0000142376.30582.ed

26. Hannan N, Beard S, Binder N, *et al*. 43 New generation antiplatelet therapies to prevent preeclampsia: Endothelial dysfunction, anti-angiogenic factors. *Pregnancy Hypertension*.2016;6:198. https:// DOI: 10.1016/j.preghy.2016.08.125

27. Norris LA, Sheppard BL, Burke G*, et al.* Platelet activation in normotensive and hypertensive pregnancies complicated by intrauterine growth retardation*. Br J Obstet Gynaecol*. 1994;101:209-214. https://doi: 10.1111/j.1471-0528.1994.tb13111.x

28. Predoi CG, Grigoriu C, Vladescu R*, et al*. Placental damages in preeclampsia - from ultrasound images to histopathological findings. *J Med Life*. 2015;8:62-65. PMID: 26366223

29. Reece MJ, Klein AA, Salviz EA, *et al.* Near-patient platelet function testing in patients undergoing coronary artery surgery: a pilot study. *Anaesthesia.* 2011;66:97-103. doi: 10.1111/j.1365-2044.2010.06608.x. PMID: 21254984.

Figure legends

Figure 1

Flowchart patient inclusion

Figure 2

Platelet count, platelet aggregation (Multiplate) and coagulation (Rotem) in preeclampsia with severe thrombocytopenia, mild thrombocytopenia, normal platelet levels compared to women with normotensive controls (controls=non-PE)

Activity: units. PE: Preeclampsia. Non-PE: Normotensive controls. PLT: Platelets. ADP: Adenosindifosfat. ASPI: Arachidonic Acid. TRAP: Thrombin activating peptide-6. Fib: Fibrinogen. CT: Clotting Time. CFT: Clot Formation time. MCF: Maximum Clot Firmness. * $p < 0.05$ for comparison women with preeclampsia vs normotensive controls. $ $p < 0.05$ for Jonckhere-Terpstra test for trends within women with preeclampsia and normal platelet levels, mild thrombocytopenia, or severe thrombocytopenia.

Table 1. Demographic characteristics

	Women with preeclampsia (n=93)	Normotensive controls (n=45)	P
Gestational age (weeks + day)	36 + 4 [33 + 0, 38+5]	40 + 1 [39 + 1, 41 +1]	< 0.001
Age (years)	31 [29, 34]	32 [29, 35]	0.029
Body mass index at booking (kg/m^2)	25.2 [21.8, 30]	23.3 [21, 26.2]	0.326
Nulliparous, n	15 (33%)	22 (49%)	<0.001
Tobacco use, n	3 (7%)	1 (2%)	0.742
Alcohol use, n	0 (0)	0 (0)	-
Delivery mode			0.006
Spontaneous vaginal delivery, n	36 (80%)	30 (67%)	

Operative vaginal delivery, n	4 (9%)	2 (4%)	
Pre-labour caesarean delivery, n	39 (87%)	7 (16%)	
Intrapartum caesarean delivery, n	14 (31%)	4 (9%)	
Intrauterine fetal death, n	1 (1%)	0 (0)	< 0.999
HELLP syndrome, n	6 (13%)	0 (0)	0.081
Eclampsia, n	0 (0)	0 (0)	-
Small-for-gestational-age neonate, n	17 (38%)	2 (4%)	0.026

Values are presented as median with interquartile range [IQR] or n (%).
HELLP, Hemolysis, Elevated Liver Enzymes, Low Platelets.

Table 2. Platelet counts, platelet aggregation and coagulation in women with preeclampsia compared to normotensive controls.

	Women with preeclampsia (n= 93)	Normotensive controls (n= 45)	P
Platelet count. x10^9/L	193 [134, 244]	234 [183, 276]	<0.001
ADP, U	62 [43, 78]	63 [51, 77]	0.541
ASPI, U	73 [55, 97]	79 [66, 102]	0.145
TRAP, U	85 [62, 104]	80 [68, 101]	0.908
Fib-MCF, mm	25 [21,27]	23 [19, 25]	0.052
Ex – CT, s	53 [49, 57]	55 [52, 59]	0.032
Ex – CFT, s	51 [43, 61]	57 [51, 63]	0.004
Ex – MCF, mm	72 [69, 74]	71 [68, 73]	0.083
In – CT, s	166 [155, 178]	169 [161, 181]	0.146
In – CFT, s	50 [44, 60]	55 [48, 64]	0.077
In – MCF, mm	71 [67, 73]	69 [66, 72]	0.368

Data presented as median with interquartile range [IQR]

ADP: Adenosine Diphosphate. ASPI: Arachidonic Acid. TRAP: Thrombin activating peptide-6. Ex: EXTEM. In: INTEM. CT: Clotting
Time. CFT: Clot Formation Time. MCF: Maximum Clot Firmness. Fib: Fibrinogen.

Table 3. Platelet aggregation and coagulation in women with one or more severe features of preeclampsia compared to women with preeclampsia without severe features.

	Preeclampsia with severe features (n=42)	**Preeclampsia without severe features (n=51)**	***P***
Platelet Count, x10^9/L	203 (122 - 229)	189 (135 - 248)	0,534
ADP, U	64 (43 - 77)	58 (42 - 81)	0,850
ASPI, U	75 (60 - 97)	72 (48 - 97)	0,442
TRAP, U	86 (66 - 107)	85 (60 - 102)	0,711
Ex - CT, s	25 (21 - 27)	25 (20 - 27)	0,972
Ex - CFT, s	54 (49 - 58)	52 (49 - 56)	0,349
Ex - MCF, mm	51 (43 - 66)	50 (43 - 60)	0,360
In - CT, s	72 (69 - 74)	72 (69 - 74)	0,650
In - CFT, s	167 (157 - 181)	162 (153 - 176)	0,146
In - MCF, mm	52 (45 - 62)	49 (43 - 59)	0,299
Fib – MCF, mm	70 (67 - 73)	71 (68 - 72)	0,441

Values are presented as median, interquartile range. Mann Whitney U test**.** * = significant
U: units. mm: millimeter. s: seconds. ADP: Adenosine Diphosphate. ASPI: Arachidonic Acid. TRAP: Thrombin Activating Peptide-6. Ex: EXTEM. In: INTEM. CT: Clotting Time. CFT: Clot Formation Time. MCF: Maximum Clot Firmness. Fib: Fibrinogen.

Highlights

- In vitro measures of coagulation were measured in women with preeclampsia.
- Platelet aggregation and thromboelastometric-assessed coagulation were assessed.
- Platelet aggregation and thromboelastic tests of coagulation are dependent on platelet counts.
- Normal platelet counts were associated with increased platelet aggregation and coagulation.
- Mild thrombocytopenia, 100-150 x 10^9 /L, affects tests of aggregation and coagulation.

Platelet aggregation and thromboelastometry monitoring in women with preeclampsia: A prospective observational study.

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