Platelet counts during normal pregnancies and pregnancies complicated with hypertensive disorders

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Running title

Platelet counts during pregnancy

Abstract

Objectives

To determine the trajectories of platelet counts and the prevalence of gestational thrombocytopenia (<150 × 10^9/L) during normal pregnancies and pregnancies with complications, such as hypertensive disorders of pregnancy (HDP), preeclampsia, and fetal growth restriction (FGR).

Study design

A multicenter retrospective study was conducted using laboratory data on women who delivered term singletons in 11 primary maternity care units between 2011 and 2018 (n = 35,045), and non-pregnant women who underwent a medical check-up between 2016 and 2019 (n = 61,189). After 1:1 matching, 28,073 pregnant women and 28,073 non-pregnant women were selected for analysis.

Main outcomes measures

The trajectories of platelet counts and prevalence of gestational thrombocytopenia were evaluated in normal pregnant women, pregnant women with complications, and non-pregnant women.

Results

The platelet counts declined throughout pregnancy state, with the nadir occurring on postpartum day 1. The platelet counts recovered to the level of the non-pregnant state at 2–7

days postpartum. The mean platelet counts at postpartum day 1 decreased by an estimated 19.8% and 9.7% compared to those in the non-pregnant state and first trimester, respectively. The prevalence of gestational thrombocytopenia in normal pregnant women at 37–41 gestational weeks and in pregnant women with complications of HDP, preeclampsia, and FGR were 6.1%, 7.3%, 17.5%, and 7.7%, respectively.

Conclusion

Platelet counts declined throughout pregnancy and recovered to the level of the non-pregnant state in the early postpartum period. Gestational thrombocytopenia is common during normal pregnancy, and its prevalence is significantly higher in women with preeclampsia.

Keywords: fetal growth restriction, gestational thrombocytopenia, hypertensive disorders of pregnancy, platelet count, preeclampsia

Abbreviations

FGR, fetal growth restrictions; HDP, hypertensive disorders of pregnancy; ITP, idiopathic thrombocytopenia purpura; PP, postpartum; SGA, small for gestational age; TTP, thrombotic thrombocytopenia purpura.

Introduction

Several reports have suggested that platelet counts during pregnancy are lower than those in non-pregnant women, and that approximately 6%–11% of normal pregnant women experience a platelet count of less than 150×10^9/L during pregnancy (1, 2). This is described as gestational thrombocytopenia if no alternative cause (e.g., preeclampsia, HELLP syndrome, idiopathic thrombocytopenic purpura [ITP], thrombotic thrombocytopenic purpura [TTP], and systemic lupus erythematosus) is identified (3, 4). This slight decrease in platelet counts may be associated with various physiological changes related to pregnancy, such as hemodilution, increased consumption due to the increased size of the spleen, and increased circulation of platelets in the placenta (3, 5, 6).

However, a previous systematic review, published in 2017, demonstrated an apparent inconsistency regarding the platelet count trajectory during pregnancy, depending on the study design (longitudinal or cross-sectional), population (race and study sample size), and stage of pregnancy (5). In addition, they could not conclude that the platelet counts during pregnancy were lower than those observed in non-pregnant women.

A recent retrospective study, published in 2018, demonstrated that platelet counts during pregnancy were lower than those in non-pregnant populations using race -, ethnic -, and

age-matched non-pregnant women and that platelet counts decreased throughout pregnancy, beginning in the first trimester (7). However, among the 4,568 normal pregnant women, only 336 women had consecutive data on platelet counts at each trimester and at the time of delivery. Although the prevalence of gestational thrombocytopenia was higher in women with pregnancy complications than in those without complications (11.9% vs. 9.9%, p=0.01), little evidence was available regarding the trajectories of platelet counts in each pregnancy complication, such as hypertensive disorders of pregnancy (HDP), preeclampsia, and fetal growth restriction (FGR).

Understanding the reference range and trajectory of platelet counts throughout pregnancy, as well as during the postpartum period enables clinicians to differentiate between normal physiological changes during pregnancy and pathological changes (e.g., ITP, TTP, preeclampsia, and HELLP syndrome). In addition, regarding platelet counts in the diagnostic criteria of preeclampsia, the definition of low platelet counts varies according to different guidelines or by country because of the lack of sufficient data on platelet counts during normal pregnancies (8-12).

Thus, the aim of this retrospective study was to determine the trajectory of platelet counts and prevalence of gestational thrombocytopenia during normal pregnancies using

clinical data from 11 maternity care units in Japan. We then compared these results with those of matched non-pregnant women. In addition, we sought to compare the trajectories of platelet counts and the prevalence of gestational thrombocytopenia between pregnancies without complications and those with placenta-associated complications, such as HDP, preeclampsia, and FGR.

Materials and Methods

We conducted a multicenter retrospective study analyzing clinical data on platelet counts in women who delivered at 37 $^{0/7}$ to 41 $^{6/7}$ gestational weeks at 11 primary maternity care units from January 2011 to December 2018. All units were located in the Aichi and Gifu Prefectures in Japan; they cared for women with low- to moderate-risk pregnancies, with each unit conducting 300–1000 deliveries annually.

This study included women who delivered term singletons at these units. To evaluate the trajectory of platelet counts during normal pregnancy, we excluded the following: preterm delivery (<37 weeks of gestation); post-term delivery (≥42 weeks of gestation); multiple pregnancy; stillbirth; presence of major congenital and chromosomal abnormalities, preexisting disorders (hematologic disease, liver disease, renal failure, autoimmune disease, collagen disease, or cancer), and pregnancy complications (gestational diabetes mellitus, HDP,

HELLP syndrome, placental abruption, placenta previa, low-lying placenta, or FGR); and incomplete data on medical records (age, height, and weight). To compare the trajectories of platelet counts between pregnancies without any complications and those with HDP and FGR among women who delivered term singletons at these units, clinical data of women with HDP and FGR were extracted for analysis.

HDP was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg during pregnancy (10). Preeclampsia was defined as hypertension with any one of the following: proteinuria (≥0.3 g/day, or ≥1+ on a urine dipstick), end-organ dysfunction (e.g., liver involvement [aspartate aminotransferase >40 IU or alanine aminotransferase >40 IU], low platelet count [$<150 \times 10^9$/L], Cr >1.0 mg/dL, and eclampsia), or uteroplacental dysfunction (i.e., FGR) after 20 weeks of gestation. In this study, FGR was defined as infants born small for gestational age (SGA); SGA was defined as birth weight and height below the 10^{th} percentile for gestational age according to a sex-specific Japanese neonatal anthropometric chart in 2000 (13).

Platelet counts were measured in EDTA-anticoagulated blood using standard automatic blood cell counters (Celltac α MEK-6500, NIHON KOHDEN Corporation, Japan). Mean platelet counts were evaluated at seven different time points: first trimester (6–12 weeks

of gestation), second trimester (13–27 weeks of gestation), first half of the third trimester (28–36 weeks of gestation), second half of the third trimester (37–41 weeks of gestation), 1 day postpartum, 2–7 days postpartum, and 3–7 weeks postpartum. The platelet counts of most women who delivered vaginally were measured at four time points (first, second, and second half of the third trimester, and 1 day postpartum). The platelet counts of women who delivered by cesarean section were measured at six time points (first, second, first and second half of the third trimester, 1 day and 2–7 days postpartum). Additional measurements were performed based on clinical needs. If multiple measurements of platelet counts were conducted during the same period, we used the first measurement for analysis. In this study, a total of 17,121 women (61.0% of final study population) had data on platelet count data at each trimester and during the postpartum period. Plausible ranges were defined as platelet counts <1,000 × 10^9/L, and outliers were excluded from further analyses. Here, we evaluated the trajectory of mean platelet counts during pregnancy and in the postpartum period in uncomplicated and complicated (HDP, preeclampsia, and FGR) pregnancies.

The clinical information extracted from each unit was anonymized and incorporated into the study for further analysis. The collected maternal information included maternal age, parity, gestational age, mode of delivery, pre-pregnancy body weight, height, and pregnancy complications (gestational diabetes mellitus, HDP, HELLP syndrome, placental abruption,

placenta previa, low-lying placenta, and FGR); neonatal information included sex, birth weight, height, and SGA.

We compared laboratory data on platelet counts in non-pregnant women (n = 61,189) who underwent a routine medical check-up from 2016 to 2019 in a medical clinic group in Aichi Prefecture, Japan with those obtained from pregnant women. The medical clinic group conducted comprehensive medical examinations for approximately 30,000 patients per year. Platelet counts were measured using an automatic clinical biochemistry analyzer (XE-2100 and XN-2000, Sysmex Corporation, Kobe, Japan; and ADVIA2120i, Siemens Healthcare, Tokyo, Japan). We excluded women with the following (n = 5,837): (1) hematologic disease, (2) anemia, (3) gastrointestinal disease, (4) hepatobiliary and pancreatic diseases, (5) renal failure, (6) cancer, (7) diabetes mellitus or hyperlipidemia, (8) thyroid disease, (9) hypertension or ischemic heart disease, (10) rheumatoid arthritis, and (11) incomplete data (age, body weight, and height). Pregnant and non-pregnant women were randomly selected at a ratio of 1:1 from 30,394 pregnant and 55,352 non-pregnant women after stratification by three factors (age, body weight, and height). The 1:1 matching was based on the categories of age (≤24, 25–29, 30–34, 35–39, and ≥40 years), body weight (<45 kg, 45–50 kg, 50–55 kg, 55–60 kg, and ≥60 kg), and height (<155 cm, 155–160 cm, 160–165 cm, and ≥165 cm).

This study was approved by the institutional ethics board of Nagoya University (approval number 2015–0415), Kishokai Medical Corporation, and Central Clinic Group. Informed consent was waived because the analysis used anonymous clinical data collected retrospectively.

Statistical analyses were performed using SPSS 27 software (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using chi-squared tests, and continuous variables were compared using the Student's *t* test or Mann-Whitney U-test. Statistical significance was set at $p < 0.05$.

Results

Among 35,045 women with laboratory data on platelet counts who delivered between 37 $^{0/7}$ to 41 $^{6/7}$ weeks of gestation at these units during the study period, a total of 30,394 women were eligible for matching, and 4,651 women were excluded (Figure 1). Among 61,189 non-pregnant women younger than 45 years of age who underwent laboratory testing between 2016 and 2019, 55,352 women were eligible for matching, and 5,837 women were excluded. After 1:1 matching based on three factors (age, weight, and height), 28,073 pregnant women and 28,073 non-pregnant women were selected for analysis.

Table 1 shows the baseline characteristics of pregnant and non-pregnant women in this study. Categories of age, body weight, and height between pregnant and non-pregnant women were equally divided.

Supplementary Figure 1 shows the distribution of platelet counts for the non-pregnant state, first (6–12 gestational weeks) and third (28–36 gestational weeks) trimesters, and postpartum day 1. The distribution of platelet counts gradually shifted to the left from the non-pregnant state to postpartum period.

Figure 2 shows the trajectory of mean platelet counts with 95% confidence interval (CI) in the non-pregnant and pregnant states as well as during the postpartum state. The platelet count in the first trimester was significantly lower than that in the non-pregnant state. The platelet counts declined throughout pregnancy, with the nadir occurring on postpartum day 1. The platelet counts recovered to the level seen in the non-pregnant state between days 2 and 7 postpartum. The mean platelet counts at postpartum day 1 decreased by an estimated 19.8% and 9.7% compared to those in the non-pregnant state and first trimester, respectively.

Table 2 shows the mean and 2.5th, 50th, and 97.5th percentiles for platelet counts as well as the prevalence of gestational thrombocytopenia ($<150 \times 10^9$/L and $<100 \times 10^9$/L) in the

non-pregnant state, during pregnancy, and in the postpartum period among the 28,073 normal pregnant women and 28,073 non-pregnant women. The prevalence of gestational thrombocytopenia (<150 × 10^9/L) was 6.1% and 8.3% in the second half of the third trimester and on postpartum day 1, respectively. The prevalence of platelet count <100 × 10^9/L was considerably rare throughout pregnancy and during the postpartum period. The lower limit (2.5th percentile) of platelet counts during normal pregnancy was 129 × 10^9/L in the second half of the third trimester.

Next, we evaluated the trajectories of mean platelet counts in women with pregnancy complications, such as HDP (n = 1,814) and FGR (n = 624). The specific types of HDP were gestational hypertension (n = 1,015), preeclampsia (n = 527), chronic hypertension (n = 238), and superimposed preeclampsia (n = 33). Figure 3 shows the trajectories of mean platelet counts with 95% CI in uncomplicated pregnancies (n = 28,073) and pregnancies complicated by HDP and preeclampsia. We found that the platelet counts in pregnant women with HDP were higher during pregnancy than those in women without any pregnancy complications; however, the platelet counts near delivery were comparable. The platelet counts in women with preeclampsia were similar to those in women with HDP during the period from the first trimester to the first half of the third trimester; however, the platelet counts in the second half of the third trimester were significantly lower. Among the 527 women with preeclampsia, 45

248 women (8.5%) presented with gestational thrombocytopenia (platelet count <150 × 10^9/L) in
249 the third trimester. Of these 45 women, 24 did not show proteinuria and were diagnosed with
250 non-proteinuric preeclampsia. In total, 79 women (15.0%) in this study were diagnosed with
251 non-proteinuric preeclampsia (low platelet count [n=24], liver involvement [n=11], renal
252 dysfunction [n=6], FGR [n=41], and eclampsia [n=3]; items are not mutually exclusive) among
253 527 women with preeclampsia. The prevalence of non-proteinuric preeclampsia diagnosed
254 with hematological adverse conditions (gestational thrombocytopenia) was 4.6% among
255 women with preeclampsia (n = 527) and 30.4% among women with non-proteinuric
256 preeclampsia (n = 79). Supplementary Table 1 shows the mean, the 2.5th, 50th, and 97.5th
257 percentiles for platelet counts, and the prevalence of gestational thrombocytopenia in pregnant
258 women with complications of HDP. Supplementary Table 2 shows the platelet counts and
259 prevalence of gestational thrombocytopenia in each type of HDP.
260
261 Figure 4 shows the trajectories of platelet counts in uncomplicated pregnancies (n =
262 28,073) and in women with pregnancies complicated with FGR (n = 624). The platelet counts
263 during pregnancy and the postpartum period were comparable between the two groups.
264 Supplementary Table 3 shows the mean, the 2.5th, 50th, and 97.5th percentiles for platelet
265 counts, and the prevalence of gestational thrombocytopenia in pregnant women with FGR.
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The prevalence of gestational thrombocytopenia was significantly higher in women with preeclampsia (17.5%, $p<0.01$) than in those with normal pregnancies (6.1%) at 37–41 weeks, while it was not significantly increased in women with HDP (7.3%, $p=0.25$) or FGR (7.7%, $p=0.38$). In contrast, the prevalence of gestational thrombocytopenia on postpartum day 1 was significantly higher in women with HDP (10.0%, $p=0.01$) and preeclampsia (14.5%, $p<0.01$) than in those with normal pregnancies (8.3%), but it was not significantly increased in women with FGR (10.0%, $p=0.14$) (Supplementary Table 1–3).

Discussion

In this multicenter retrospective study, we demonstrated the trajectories of platelet counts and the reference range during pregnancy and the postpartum period. Our main findings of this study were that platelet counts declined throughout pregnancy, with the nadir occurring at postpartum day 1, and that the platelet counts returned to the level of the non-pregnant state between days 2 and 7 postpartum. The prevalence of gestational thrombocytopenia (platelet count $<150 \times 10^9$/L) in normal pregnancy was 6%–8% at term and postpartum period, while it increased to 7%–17% in pregnant women with complications of HDP, preeclampsia, and FGR. In addition, we found that the prevalence of non-proteinuric preeclampsia diagnosed with gestational thrombocytopenia was 4.6% among women with preeclampsia.

Our study results were consistent with those of previous studies demonstrating that platelet counts during pregnancy were lower than those in the non-pregnant state and that they decreased throughout pregnancy (7, 14). We found that the average decline in the mean platelet count during normal pregnancy was approximately 20% from the non-pregnant state to postpartum day 1, which was similar to values obtained in previous studies (20.5% and 21.7%, respectively) (7, 14). In addition, approximately half of the total decline had already occurred during the first trimester. However, whether the underlying mechanism of rapid decline during the first trimester is due to either physiological changes associated with pregnancy or the study design issue remains uncertain. There is a possibility that this could be explained by the fact that we could not compare platelet counts between the pregnant and non-pregnant states in the same individual; however, we selected the matched non-pregnant women by using three factors to reduce selection bias risk. Further research is required to elucidate the mechanisms underlying the rapid decline in platelet counts.

Understanding the laboratory changes accompanying the different trimesters during normal pregnancy is important for clinicians to facilitate early recognition and timely diagnosis, manage gestational thrombocytopenia, and differentiate between normal physiological changes related to pregnancy and pathological changes. In addition, the reference range of platelet counts in normal pregnancy may be of value for the establishment of diagnostic criteria for

preeclampsia because the definition of low platelet counts in the diagnosis of preeclampsia differs based on the guidelines used and the country. Several guidelines, including those of the International Society for the Study of Hypertension in Pregnancy, the Japan Society of Obstetrics and Gynecology, and the Royal College of Obstetricians and Gynaecologists, define a low platelet count as $<150 \times 10^9$/L in the diagnosis of preeclampsia, while the guidelines of the American College of Obstetricians and Gynecologists define $<100 \times 10^9$/L as the cutoff; the guidelines of the Society of Obstetricians and Gynaecologists of Canada define $<50 \times 10^9$/L as the threshold (9-12). According to our study, the lower limit of the normal range (2.5th percentile) was 152×10^9/L, 140×10^9/L, and 129×10^9/L at 13–27, 28–36, and 37–41 gestational weeks, respectively. Thus, there were possibly more normal women who were diagnosed with non-proteinuric preeclampsia due to lower platelet counts during the third trimester compared with those in the second trimester. Considering the change in the lower limit of platelet counts according to the trimester, we could understand the difference in the pathological implication even if the platelet counts were the same in different trimesters (e.g., 140×10^9/L at 10 gestational weeks vs. 140×10^9/L at 40 gestational weeks).

In this study, the platelet counts in women with HDP were significantly higher before the onset of HDP, especially during the first and second trimesters, than those in women without any pregnancy complications. This is consistent with a previous study (15); however,

consensus has yet to be reached. Although the underlying mechanisms of increased platelet counts in women with HDP remain unclear, possible explanations are as follows: [1] women who will develop HDP may have a potential risk for systemic chronic inflammation (16, 17), which contributes to the activation and increase of platelets (18, 19); and [2] platelet counts are known to be positively associated with BMI and body weight (20, 21). Thus, the difference in baseline characteristics regarding physique between normal pregnancies and HDP may affect platelet counts. In fact, we found that the pre-pregnancy body weight and BMI in normal pregnancies and HDP in this study were 51.9 ± 7.9 kg and 56.7 ± 11.3 kg (p <0.001), and 20.8 kg/m^2 and 22.7 kg/m^2 (p <0.001), respectively. To reduce these differences, we randomly selected women without any complications and with HDP at a ratio of 2:1 after stratification by three factors: maternal age, height, and pre-pregnancy body weight. The platelet counts in the normal pregnant women and women with HDP at 6–12 weeks and 13–27 weeks were 243 ± 48 × 10^9/L and 249 ± 49 × 10^9/L, and 236 ± 48 × 10^9/L and 242 ± 49 × 10^9/L, respectively. The difference in platelet counts between the two groups was significantly decreased by stratification matching; however, there was still a significant difference (approximately 6 × 10^9/L), indicating that the underlying mechanisms of increased platelet counts in women with HDP may have been mainly associated with systemic chronic inflammation. However, further studies are needed to elucidate the underlying mechanism.

The strengths of this study were that the sample size was much larger than that of prior studies (7, 14), and a total of 17,121 women (61.0%) had consecutive data on platelet counts at each trimester and postpartum period. In addition, we evaluated platelet counts at seven time periods and compared them between women with uncomplicated pregnancies and pregnant women with different complications. Finally, with the larger population size and more centers where the clinical data were obtained, the generalizability of this study was increased compared to that of previous studies. Furthermore, we compared platelet counts between pregnant and non-pregnant women after adjusting for age, weight, and height.

Several limitations of this study should be acknowledged. First, we excluded women who did not deliver at the 11 specified maternity care units; thus, we could not deny the possibility that women with severe thrombocytopenia may have been referred to higher-level facilities before delivery because these 11 maternity care units cared only for low-risk pregnancies and did not have a blood bank on site. As previously described, we could not compare platelet counts between non-pregnant and pregnant states in the same individual.

In conclusion, platelet counts declined throughout pregnancy and recovered to the level observed in the non-pregnant state in the early postpartum period. Gestational thrombocytopenia was common during normal pregnancy and the postpartum period, while its

prevalence before delivery was significantly higher in pregnant women with preeclampsia. Understanding the trajectory of platelet counts may facilitate the differentiation between normal physiological changes related to pregnancy and pathological changes.

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References

1. Boehlen F, Hohlfeld P, Extermann P, Perneger TV, de Moerloose P. Platelet count at term pregnancy: a reappraisal of the threshold. Obstetrics and gynecology. 2000;95(1):29-33.
2. Burrows RF, Kelton JG. Fetal thrombocytopenia and its relation to maternal thrombocytopenia. The New England journal of medicine. 1993;329(20):1463-6.
3. ACOG Practice Bulletin No. 207: Thrombocytopenia in Pregnancy. Obstetrics and gynecology. 2019;133(3):e181-e93.
4. Myers B. Diagnosis and management of maternal thrombocytopenia in pregnancy. British journal of haematology. 2012;158(1):3-15.
5. Reese JA, Peck JD, McIntosh JJ, Vesely SK, George JN. Platelet counts in women with normal pregnancies: A systematic review. American journal of hematology. 2017;92(11):1224-32.
6. Ciobanu AM, Colibaba S, Cimpoca B, Peltecu G, Panaitescu AM. Thrombocytopenia in Pregnancy. Maedica. 2016;11(1):55-60.

7. Reese JA, Peck JD, Deschamps DR, McIntosh JJ, Knudtson EJ, Terrell DR, et al. Platelet Counts during Pregnancy. The New England journal of medicine. 2018;379(1):32-43.
8. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. Obstetrics and gynecology. 2019;133(1):e1-e25.
9. Webster K, Fishburn S, Maresh M, Findlay SC, Chappell LC. Diagnosis and management of hypertension in pregnancy: summary of updated NICE guidance. BMJ (Clinical research ed). 2019;366:l5119.
10. Makino S, Takeda J, Takeda S, Watanabe K, Matsubara K, Nakamoto O, et al. New definition and classification of "Hypertensive Disorders of Pregnancy (HDP). Hypertension Research in Pregnancy. 2019;7(1):1-5.
11. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. Hypertension. 2018;72(1):24-43.
12. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy: executive summary. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC. 2014;36(7):575-6.
13. Itabashi K, Miura F, Uehara R, Nakamura Y. New Japanese neonatal anthropometric charts for gestational age at birth. Pediatrics international : official journal of the Japan Pediatric Society. 2014;56(5):702-8.
14. Li-Xia Z, Ning D, Rui-Xia Y, Ang L, Xuan-Mei L, Nan Y, et al. Platelet counts during pregnancy in Chinese women. Journal of Laboratory Medicine. 2020(0):20190142.
15. Örgül G, Aydın Haklı D, Özten G, Fadiloğlu E, Tanacan A, Beksaç MS. First trimester complete blood cell indices in early and late onset preeclampsia. Turkish journal of obstetrics and gynecology. 2019;16(2):112-7.
16. Borzychowski AM, Sargent IL, Redman CW. Inflammation and pre-eclampsia. Semin Fetal Neonatal Med. 2006;11(5):309-16.
17. Redman CW, Sargent IL. Preeclampsia and the systemic inflammatory response. Semin Nephrol. 2004;24(6):565-70.
18. Stokes KY, Granger DN. Platelets: a critical link between inflammation and microvascular dysfunction. J Physiol. 2012;590(5):1023-34.
19. Koupenova M, Clancy L, Corkrey HA, Freedman JE. Circulating Platelets as Mediators of Immunity, Inflammation, and Thrombosis. Circ Res. 2018;122(2):337-51.
20. Samocha-Bonet D, Justo D, Rogowski O, Saar N, Abu-Abeid S, Shenkerman G, et al. Platelet counts and platelet activation markers in obese subjects. Mediators Inflamm. 2008;2008:834153.
21. Coban E, Ozdogan M, Yazicioglu G, Akcit F. The mean platelet volume in patients with obesity. International Journal of Clinical Practice. 2005;59(8):981-2.

425

426 **Figure legends**

427 Figure 1. Flow diagram of the study population. Laboratory data on platelet counts were
428 collected for 35,045 pregnant women and 61,189 non-pregnant women. After 1:1 matching to
429 adjust for three factors (age, weight, and height), a total of 28,073 pregnant women and 28,073
430 non-pregnant women were selected for analysis. * indicates items not mutually exclusive.

431

432 Figure 2. Trajectory of mean platelet counts when non-pregnant, during pregnancy, and at the
433 postpartum periods. Mean platelet counts with 95% confidence interval at non-pregnant state
434 and four prenatal (6–12 weeks, 13–27 weeks, 28–36 weeks, and 37–41 weeks) and three
435 postpartum (postpartum day 1, days 2–7, and weeks 3–7) periods are shown. PP, postpartum.

436

437 Figure 3. Trajectories of mean platelet counts in normal pregnant women and women with
438 pregnancy complicated by HDP and preeclampsia. Mean platelet counts with 95% confidence
439 interval at four prenatal and three postpartum periods are shown. HDP, hypertensive disorders
440 of pregnancy; PP, postpartum.

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442 Figure 4. Trajectories of platelet counts in normal pregnant women and women with
443 pregnancies complicated with FGR. Mean platelet counts with 95% confidence interval at four
444 prenatal and three postpartum periods are shown. FGR, fetal growth restrictions; PP,

445 postpartum.

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447 Supplementary Figure 1. The distributions of platelet counts during the non-pregnant state, first

448 and third trimesters, and the postpartum period.

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Table 1. Baseline characteristics of pregnant and non-pregnant women

Characteristics	Pregnant women n = 28,073	Non-pregnant women n = 28,073
Maternal characteristics		
Maternal age (years)	30.8 ± 4.9	30.8 ± 5.2
Category of maternal age		
<25 years	2,698	2,698
25–29 years	9,068	9,068
30–34 years	9,484	9,484
35–39 years	5,879	5,879
≥40 years	944	944
Gestational age at delivery (weeks)	39.6 ± 1.2	
Cesarean section (%)	4,057/27,525 (14.7)	
Primipara (%)	13,968/28,073 (49.8)	
Pre-pregnancy body weight (kg)	51.9 ± 7.9	52.5 ± 8.6
Category of body weight		
<45 kg	4,144	4,144
45–50 kg	7,844	7,844
50–55 kg	7,700	7,700
55–60 kg	4,370	4,370
≥60 kg	4,015	4,015
Height (cm)	158 ± 5.4	159 ± 5.4
Category of height		
<155 cm	7,082	7,082
155–160 cm	9,695	9,695
160–165 cm	7,985	7,985
≥165 cm	3,311	3,311
Neonatal characteristics		
Male (%)	14,139/27,635 (51.2)	
Birth weight (g)	3,100 ± 354	
Height (cm)	49.8 ± 1.6	

Date are shown as mean ± standard deviation, or n (%).

Table 2. The mean and 2.5th, 50th, and 97.5th percentiles for platelet counts and the prevalence of gestational thrombocytopenia at non-pregnant state, during pregnancy, and postpartum period.

	non-pregnant n = 28,073	6–12 wk n = 18,534	13–27 wk n = 21,546	28–36 wk n = 26,825	37–41 wk n = 5,091	PP 1 day n = 26,931	PP 2–7 day n = 4,809	PP 3–7 wk n = 626
Average time point		GA 10.9 wk	GA 23.8 wk	GA 31.5 wk	GA 37.7 wk	PP 1 day	PP 4.5 day	PP 4.8 wk
Platelet counts								
Mean ± SD ($\times 10^9$/L)	268 ± 58	238 ± 48	231 ± 47	225 ± 49	221 ± 53	215 ± 52	261 ± 65	244 ± 61
2.5th percentile ($\times 10^9$/L)	170	155	152	140	129	127	149	148
50th percentile ($\times 10^9$/L)	260	234	227	221	218	210	257	233
97.5th percentile ($\times 10^9$/L)	400	341	335	335	337	328	403	386
<150 ($\times 10^9$/L)	196 (0.7)	343 (1.9)	474 (2.2)	1,172 (4.4)	309 (6.1)	2,224 (8.3)	127 (2.6)	19 (3.0)
<100 ($\times 10^9$/L)	22 (0.1)	13 (0.7)	8 (0.0)	22 (0.1)	16 (0.3)	81 (0.3)	12 (0.2)	0 (0)

GA, gestational age; PP, postpartum. Data on the prevalence of gestational thrombocytopenia are shown as n (%).

Supplementary Table 1. The mean and 2.5th, 50th, and 97.5th percentiles for platelet counts and the prevalence of gestational thrombocytopenia during pregnancy and postpartum period in women with hypertensive disorders of pregnancy.

	6–12 wk n = 1,229	13–27 wk n = 1,449	28–36 wk n = 1,700	37–41 wk n = 532	PP 1 day n = 1,700	PP 2–7 day n = 537	PP 3–7 wk n = 55
Average time point	GA 10.8 wk	GA 23.7 wk	GA 31.3 wk	GA 38.1 wk	PP 1 day	PP 4.5 day	PP 4.7 wk
Platelet counts							
Mean ± SD ($\times 10^9$/L)	250 ± 50	243 ± 49	237 ± 51	226 ± 57	216 ± 56	270 ± 70	271 ± 84
2.5th percentile ($\times 10^9$/L)	170	161	153	121	119	146	171
50th percentile ($\times 10^9$/L)	246	240	232	222	211	268	267
97.5th percentile ($\times 10^9$/L)	358	344	353	348	338	414	496
<150 ($\times 10^9$/L)	6 (0.5)	19 (1.3)	31 (1.8)	39 (7.3)	170 (10.0)	18 (3.4)	0 (0)
<100 ($\times 10^9$/L)	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.4)	14 (0.8)	4 (0.7)	0 (0)

GA, gestational age; PP, postpartum. Data on the prevalence of gestational thrombocytopenia are shown as n (%).

Supplementary Table 2. The mean and 2.5th, 50th, and 97.5th percentiles for platelet counts and the prevalence of gestational thrombocytopenia during pregnancy and postpartum period in women with HDP classified into four types.

	6–12 wk	13–27 wk	28–36 wk	37–41 wk	PP 1 day	PP 2–7 day	PP 3–7 wk
Gestational hypertension	n = 687	n= 816	n = 972	n = 270	n = 978	n = 275	n = 34
Mean ± SD ($\times 10^9$/L)	248 ± 51	242 ± 48	236 ± 49	236 ± 52	218 ± 54	275 ± 68	272 ± 74
2.5th percentile ($\times 10^9$/L)	169	162	155	154	129	150	170
50th percentile ($\times 10^9$/L)	243	239	231	230	212	2672	271
97.5th percentile ($\times 10^9$/L)	363	342	345	356	341	421	435
<150 ($\times 10^9$/L)	3 (0.4)	13 (1.6)	12 (1.2)	0 (0)	82 (8.4)	6 (2.2)	0 (0)
<100 ($\times 10^9$/L)	0 (0)	1 (0.1)	1 (0.1)	0 (0)	5 (0.5)	1 (0.4)	0 (0)
Preeclampsia	n = 348	n = 419	n = 503	n = 211	n = 501	n = 192	n = 18
Mean ± SD ($\times 10^9$/L)	248 ± 47	242 ± 49	235 ± 55	207 ± 56	205 ± 57	258 ± 73	248 ± 52
2.5th percentile ($\times 10^9$/L)	170	161	145	111	107	116	1786
50th percentile ($\times 10^9$/L)	245	237	229	208	198	258	245
97.5th percentile ($\times 10^9$/L)	351	346	358	317	328	386	340
<150 ($\times 10^9$/L)	3 (0.9)	5 (1.2)	17 (3.4)	37 (17.5)	73 (14.5)	11 (5.7)	0 (0)
<100 ($\times 10^9$/L)	1 (0.3)	0 (0)	0 (0)	2 (0.9)	9 (1.8)	3 (1.6)	0 (0)
Chronic hypertension	n = 167	n = 181	n = 192	n = 38	n = 193	n = 57	n = 2
Mean ± SD ($\times 10^9$/L)	262 ± 51	249 ± 50	243 ± 52	245 ± 62	229 ± 55	279 ± 58	442 ± 30
2.5th percentile ($\times 10^9$/L)	174	167	166	148	130	181	242
50th percentile ($\times 10^9$/L)	256	251	238	235	226	270	442
97.5th percentile ($\times 10^9$/L)	368	361	358	384	339	394	642
<150 ($\times 10^9$/L)	0 (0)	0 (0)	1 (0.5)	2 (5.3)	12 (6.2)	1 (1.8)	0 (0)
<100 ($\times 10^9$/L)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Superimposed preeclampsia	n = 27	n = 33	n = 33	n = 13	n = 28	n = 13	n = 1
Mean ± SD ($\times 10^9$/L)	250 ± 47	246 ± 46	243 ± 46	237 ± 49	232 ± 59	309 ± 78	291
2.5th percentile ($\times 10^9$/L)	166	151	155	184	121	221	291
50th percentile ($\times 10^9$/L)	247	243	246	212	239	287	291
97.5th percentile ($\times 10^9$/L)	333	321	326	328	334	473	291
<150 ($\times 10^9$/L)	0 (0)	1 (3.0)	1 (3.0)	0 (0)	3 (10.7)	0 (0)	0 (0)
<100 ($\times 10^9$/L)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

GA, gestational age; PP, postpartum. Data on the prevalence of gestational thrombocytopenia are shown as n (%).

Supplementary Table 3. The mean and 2.5th, 50th, and 97.5th percentiles for platelet counts and the prevalence of gestational thrombocytopenia during pregnancy and postpartum period in women with fetal growth restriction.

	6–12 wk n = 418	13–27 wk n = 526	28–36 wk n = 1,052	37–41 wk n = 183	PP 1 day n = 613	PP 2–7 day n = 151	PP 3–7 wk n = 13
Average time point	GA 10.9 wk	GA 23.9 wk	GA 33.3 wk	GA 37.8 wk	PP 1 day	PP 4.7 day	PP 5.0 wk
Platelet counts							
Mean ± SD ($\times 10^9$/L)	236 ± 51	235 ± 49	229 ± 53	214 ± 51	214 ± 54	262 ± 69	231 ± 62
2.5th percentile ($\times 10^9$/L)	152	152	142	105	125	156	134
50th percentile ($\times 10^9$/L)	232	230	224	213	207	253	227
97.5th percentile ($\times 10^9$/L)	345	336	340	314	334	416	344
<150 ($\times 10^9$/L)	10 (2.4)	9 (1.7)	44 (4.2)	14 (7.7)	61 (10.0)	3 (2.0)	1 (7.7)
<100 ($\times 10^9$/L)	1 (0.2)	3 (0.6)	6 (0.6)	5 (2.7)	3 (0.5)	1 (0.7)	0 (0)

GA, gestational age; PP, postpartum. Data on the prevalence of gestational thrombocytopenia are shown as n (%).