RBMO

ELSEVIER

ARTICLE

Thrombocytopaenia and COVID-19 infection during pregnancy increases the risk of preeclampsia: a multicentre study

BIOGRAPHY

Dr Marcelino Pérez is Principal Investigator of the SONEV Research Group, Catholic University of Valencia, Spain. He is a senior statistician in the Department of Epidemiology, Public Health and Biostatistics, and has extensive experience in the design and statistical analysis of clinical and epidemiological studies.

Marta Defez-Martin[1], María Inmaculada Martín-Díaz[2], Sandra Atienza-Ramirez[3], Francisco Llorca-Colomer[4], Maria Teresa Murillo-Llorente[4], Marcelino Perez-Bermejo[4,*]

KEY MESSAGE

Although COVID-19 infection does not seem to be a risk factor for low platelet counts in pregnant women, the risk is increased with smoking and in women with Rh negative blood group B. In case of pregnancy with thrombocytopaenia, COVID-19 infection carries an increased risk of preeclampsia.

ABSTRACT

Research question: Is a low platelet count related to an increased risk of severe disease in pregnant women with active severe acute respiratory syndrome coronavirus 2 infection?

Design: A cross-sectional multicentre study in pregnant women with COVID-19 confirmed by polymerase chain reaction, antigen test, antibody test, or all.

Results: A total of 153 pregnant women with COVID-19 were included in the study, of whom 12.4% had thrombocytopaenia. Pregnant women with thrombocytopaenia were on average 3.1 years older (95% CI 0.18 to 6.38) than women without thrombocytopaenia. Pregnant smokers had a higher risk of thrombocytopaenia than non-smokers (OR 6.55, CI 95% 1.29 to 33.13). B Rh negative (B Rh–) pregnant women had a much higher risk of thrombocytopaenia than pregnant women with other blood groups (OR 16.83, CI 95% 1.42 to 199.8). Pregnant women with thrombocytopaenia had a much higher risk of suffering from preeclampsia (OR 16.2, CI 95% 1.35 to 193.4).

Conclusions: COVID-19 infection is not a risk factor for a low platelet count in pregnant women, although the risk is increased by smoking and in women with blood group B Rh–. In case of pregnancy with thrombocytopaenia, COVID-19 infection leads to an increased risk of preeclampsia.

[1] School of Medicine and Health Sciences, Catholic University of Valencia, Calle Quevedo, 2, Valencia 46001, Spain
[2] Hospital Clínico Universitario de Valencia, Valencia, Spain
[3] Hospital Universitario Dr Peset, Valencia, Spain
[4] SONEV Research Group, School of Medicine and Health Sciences, Catholic University of Valencia, Calle Quevedo, 2, Valencia 46001, Spain

*Corresponding author. E-mail address: marcelino.perez@ucv.es (M. Perez-Bermejo). https://doi.org/10.1016/j.rbmo.2022.11.001 1472-6483/
Declaration: The authors report no financial or commercial conflicts of interest.

INTRODUCTION

In late 2019, numerous cases of bilateral pneumonia of unknown cause were first detected in the Chinese city of Wuhan. The causative agent was subsequently identified to be a new type of coronavirus (*WHO, 2019*; *Huang et al., 2020*). The International Committee on Taxonomy of Viruses named it 'severe acute respiratory syndrome coronavirus 2,' (SARS-CoV-2), as it is related to the virus that caused the 'severe acute respiratory syndrome' (SARS) pandemic in 2003 (*Gorbalenya et al., 2020*). On 30 January 2020, the World Health Organization (WHO) declared the new coronavirus pneumonia epidemic a public health emergency of international concern (*Shrivastava and Shrivastava, 2020*). On 11 February 2020, the WHO announced that the official name of the disease would be 'COVID-19', a shortened version of 'coronavirus disease 2019' (*WHO, 2020*).

Its main routes of transmission are through small respiratory droplets containing the virus, either by inhalation (*Dashraath et al., 2020*) or by contact with mucous membranes. Transmission is also possible by inhalation of aerosols and by objects on which the virus has been deposited (*Wax and Christian, 2020*).

The most common symptoms are fever, cough, tiredness and loss of taste or smell. The most severe symptoms are respiratory distress, loss of speech or mobility, as well as confusion and chest pain (*Guan et al., 2020*; *Xu et al., 2020*). On admission, between 63% and 83% of patients had lymphopaenia, and up to 36% had thrombocytopaenia, with 5% having platelet counts less than $100{,}000 \times 10^9$/l. Thirty-seven per cent of patients had elevated serum glutamic-oxaloacetic transaminase (aspartate aminotransferase) levels and 21% had elevated serum glutamic pyruvic transaminase (alanine aminotransferase) levels. Elevated C-reactive protein levels were found in up to 60.7% of patients, and elevated D-dimer in up to 46.4% (*Huang et al., 2020*).

During the course of a normal pregnancy, the body undergoes physical and psychological changes, focused on adapting and adjusting to the demands of the development of a human being inside the woman's uterus. These changes take place progressively (*Xu et al., 2020*).

At the cardiovascular level, blood volume increases and blood is redistributed to send more flow to the uterus and placenta, up to 25% of the cardiac output. Cardiac output increases by up to 50% between the 16th and 20th week of pregnancy. On the other hand, blood pressure decreases physiologically to compensate for these increases, reaching its lowest point between 16 and 20 weeks, and then gradually increasing to practically normal figures in the last trimester. This decrease in blood pressure is caused by increased levels of nitric oxide, progesterone and relaxin, which decrease vascular smooth muscle tone (*Kazma et al., 2020*).

During gestation, erythrocytes increase as a result of increased erythropoietin production but in lesser proportion to the increase in plasma volume; therefore, haemoglobin concentration decreases. Dilutional anaemia occurs, with a decrease of 1–2 g/dl of haemoglobin in the second trimester, stabilizing in the third trimester (*Chandra et al., 2021*).

A physiological decrease occurs in the platelet count during pregnancy owing to haemodilution, increased consumption in peripheral tissues and increased aggregation caused by elevated thromboxane A2. Physiological thrombocytopaenia is moderate and not related to maternal or fetal effects; however, if it is related to other pathologies, it may have consequences on maternal–fetal health and require specific monitoring and treatment. Gestational thrombocytopaenia accounts for 70–80% of cases of thrombocytopaenia in pregnancy, hypertensive disorders for 20% and immune thrombocytopaenic purpura for 3–4% (*Ciobanu et al., 2016*).

COVID-19 has been associated with an increased risk of severe disease in elderly patients and those with chronic comorbidities. Studies of previous pandemics and influenza virus suggest that pregnant women may be at increased risk of morbidity and mortality associated with infection (*Narang et al., 2020*). Physiological changes during pregnancy include increased heart rate and oxygen consumption, decreased lung capacity, increased clotting factors and decreased cellular immunity, which may increase the risk of more severe disease compared with healthy adults (*Mertz et al., 2013*), as well as dysregulation of ACE2, the pathway used by SARS-CoV-2, to enter the cell. Binding of SARS-CoV-2 to ACE2 decreases angiotensin 1-7 levels, which worsens the vasoconstriction, inflammation and procoagulant effects that occur in preeclampsia. Therefore, some studies have suggested that preeclampsia may be common in pregnant women with COVID-19 (*Boushra et al., 2021*).

Thrombocytopaenia seems to be common in non-pregnant women hospitalized with COVID-19 (*Xu et al., 2020*). Limited research on thrombocytopaenia in pregnant women with COVID-19 has been conducted; therefore, insufficient studies are available on which to establish a solid basis for a higher incidence. Also, evidence that this is indicative of a more severe evolution of the infection is lacking (*Kim et al., 2020*; *Le Gouez et al., 2020*; *Rasmussen et al., 2020*). Some studies, however, have established a relationship between a lower platelet count and a greater severity of the disease, as well as mortality in non-pregnant women (*Lippi et al., 2020*).

Other causes that produce moderate to severe thrombocytopaenia, such as gestational thrombocytopaenia, preeclampsia, HELLP syndrome and immune thrombocytopaenia, among others, must be taken into account (*Zitiello et al., 2020*).

Platelet transformation during preeclampsia includes the following: thrombocytopaenia, increased volume and increased platelet microaggregates (may precede the onset of the disease), and an increase in the activity of thromboglobulin (platelet factor 4), which is considered an expression of platelet activity when related to 24-h protein levels. It has been suggested that this entity presents with an increase in platelet consumption, to which the imbalance between thromboxane, prostacyclin and nitric oxide contributes, with predominance of the aggregating power of the former. For some, platelet damage is a trigger and not a result. In addition, the alteration of placental circulation is a reason for platelet stimulation, through the increase of frictional stress and inadequate trophoblastic invasion with abnormal arterial flow (*Adelborg et al., 2021*).

It is important to conduct a platelet study before administering neuroaxial analgesia

as up to one-third of patients with COVID-19 present thrombocytopaenia, compared with 7–12% of pregnant patients without concurrent infection (*Bauer et al., 2020*). Although the platelet count may be altered in pregnant women with COVID-19, neuroaxial analgesia administered during labour is allowed. If the platelet count is extremely low, however, administration is contraindicated until platelet values are increased to a safe range (*Tang et al., 2020*).

Several hypotheses about thrombocytopaenia have been presented in pregnant women with Covid-19: direct infection of bone marrow cells; destruction of haematopoietic progenitors by cytokine storm; destruction of platelets by immune complexes and induction of autoantibodies; lung damage itself; increased platelet consumption; and induced by certain drugs (ribavirin, fluoroquinolones and hydroxychloroquine) (*Kim et al., 2020*; *Zhang et al., 2020*).

Owing to the paucity of studies and the different existing hypotheses, it was considered necessary to analyse this subject in further depth. Therefore, in the present study, the relationship between thrombocytopaenia in pregnant women and COVID-19, its prevalence, its possible causes and the influence it has on the severity of the disease, as well as possible gestational complications, were examined.

MATERIALS AND METHODS

Participants

A cross-sectional study was conducted in pregnant women with COVID-19 at the Dr Peset University Hospital in Valencia, Spain, La Fe University and Polytechnic Hospital in Valencia, Spain, and the General University Hospital in Castellón, Spain. Ethics approval from the Research Ethics Committee of each of the three hospitals was obtained before conducting the study (Dr Peset University Hospital: approval code 142/20 dated 17 December 2020; General University Hospital in Castellón: approval code January 2021, dated 25 January 2021; La Fe University and Polytechnic Hospital: approval code 2021-247-1, dated 28 April 2021. The work was carried out in accordance with the World Medical Association's Declaration of Helsinki, and written informed consent was obtained from all patients.

The inclusion criteria were pregnant women with COVID-19 confirmed by polymerase chain reaction, antigen test, antibody test, or all, who agreed to participate in the study after the study protocol had been explained to them. Under-age pregnant women were excluded. Diagnosis of HELLP syndrome or other microangiopathy of pregnancy was also considered as exclusion criteria. After applying these criteria, a total of 153 pregnant women with COVID-19 were included in the study.

For the analysis of thrombocytopaenia, the definition of a platelet count of less than 150,000 platelets per microlitre of blood was taken into account (*American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics, 2016*).

Statistical analysis

The Kolmogorov–Smirnov goodness-of-fit test was used to study the normality of the data distribution. Quantitative data are presented using central tendency and dispersion statistics and qualitative variables are expressed as absolute value and percentage (%).

Student's t-test or analysis of variance were used to compare the values of continuous variables. Pearson's correlation coefficient was used to establish the relationship between continuous variables, and chi-squared test and odds ratio were used to establish the association between categorical variables.

For all tests, a significance level of less than 0.05 was accepted in bilateral comparison. IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp, Armonk, NY, USA) was used for data analysis.

RESULTS

After data collection, 153 pregnant women with COVID-19 were included in the study, of whom 12.4% had thrombocytopaenia. The results referring to the characteristics of the pregnant women under study are presented in TABLE 1.

The age of women with thrombocytopaenia was significantly higher (Student's t-test; $P = 0.024$) than those without. Pregnant women with thrombocytopaenia were on average 3.1 years older (95% CI 0.18 to 6.38) than those without.

A statistically significant association was found between smoking and thrombocytopaenia (chi-squared test; $P = 0.011$). Pregnant smokers had 6.55 times higher risk of thrombocytopaenia than pregnant non-smokers (95% CI 1.29 to 33.13). Similarly, a statistically significant association was found between blood group and thrombocytopaenia (chi-squared test; $P = 0.005$). Pregnant women with blood group B Rh– had a 16.83 times higher risk of thrombocytopaenia than those with other blood groups (95% CI 1.42 to 199.8). A statistically significant association was also found between preeclampsia and thrombocytopaenia (chi-squared test; $P = 0.004$). Pregnant women with thrombocytopaenia had 16.2182 times higher risk of preeclampsia than those without (95% CI 1.35 to 193.4). No association, however, was found between thrombocytopaenia and gestational diabetes or the different APGAR scores of newborn babies.

The relationship between thrombocytopaenia and maternal haemoglobin, urea, creatinine and liver

TABLE 1 SOCIODEMOGRAPHIC CHARACTERISTICS OF THE SAMPLE

Characteristics	Thrombocytopaenia	Mean (SD) or *n* (%)	*P*-value
Thrombocytopaenia		19 (12.4)	
Dr Peset Hospital, Valencia		49 (32)	
La Fe Hospital, Valencia		49 (32)	
General Hospital, Castellón		55 (36)	
Gestational age (COVID date), days		219.7 (74.8)	
Gestational age (delivery), days		272.0 (18.4)	
Age, years		32.3 (5.72)	
Age, years	No	31.9 (5.97)	0.024[a]
	Yes	35.0 (4.44)	

[a] Student's t-test.

TABLE 2 RELATIONSHIP BETWEEN THROMBOCYTOPAENIA AND OTHER MATERNAL ANALYTICAL VARIABLES BEFORE COVID-19, DURING INFECTION AND AFTER COVID-19

Variables	Thrombocytopaenia	Infectious period	*P*-value[a]
		Mean (SD)	
Maternal haemoglobin, g/dl	No	9.4 (5.14)	0.172
	Yes	12.0 (1.3)	
Maternal red blood cells, 10^6/µl	No	3.55 (3.79)	0.276
	Yes	3.98 (0.55)	
Maternal urea, mg/dl	No	11.6 (9.3)	0.006[b]
	Yes	20.6 (6.6)	
Maternal creatinine, mg/dl	No	0.40 (0.28)	0.339
	Yes	0.66 (0.09)	
Total bilirubin, mg/dl	No	0.18 (0.23)	0.003[b]
	Yes	0.32 (0.20)	
Maternal SGOT, UI/l	No	5.9 (11.4)	0.224
	Yes	12.29 (7.4)	
Maternal SGPT, UI/l	No	12.18 (3.22)	0.801
	Yes	17.5 (4.65)	
Maternal GGT, U/l	No	3.14 (2.7)	0.801
	Yes	4.50 (7.21)	

[a] Student's t-test.

[b] Statistically significant.GGT, gamma-glutamyl transferase; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

function during the infectious period is presented in TABLE 2. Statistically significant increases were found in urea ($P = 0.006$) and bilirubin ($P = 0.003$) in the women under study during the infectious period.

A statistically significant decrease in platelets was observed from the first to the second trimester, as well as from the second to the third trimester (paired student's t-test; $P = 0.009$). This effect is presented in FIGURE 1.

No association was found between thrombocytopaenia and preterm delivery (chi-squared test; $P = 0.816$). No significant differences were found between maternal age and preterm delivery (Student's t-test; $P = 0.983$). Similarly, no significant difference was found between platelet counts and preterm delivery (Student's t-test; $P = 0.626$).

Statistically significant differences were found in the first-trimester platelet counts of women who had low haemoglobin (Student's t-test; $P = 0.003$). These women had, on average, 39.53 × 10^9/l more platelets (95% CI 13.45 to 65.61).

In pregnant women who had low haemoglobin in the infectious period, statistically significant increases were found in the platelet count in the second (Student's t-test; $P = 0.003$) and third trimester (Student's t-test; $P = 0.037$). In the second, those with low haemoglobin had on average 41.69 × 10^9/l (95% CI 15.01 to 68.38) and in the third, on average 49.04 × 10^9/l (95% CI 2.97 to 95.1).

A statistically significant positive correlation was found between platelet count in the infectious period and haemoglobin in the same period (rho = 0.442; $P = 0.036$). Similarly, a statistically significant positive correlation was found between infectious period lymphocytes and infectious period haemoglobin (rho = 0.527; $P < 0.001$). No correlation was found between platelet count and haemoglobin.

As seen above, a statistically significant association was found between blood group and thrombocytopaenia (chi-squared test; $P = 0.005$). Pregnant women with blood group B Rh– had a 16.83 times higher risk of thrombocytopaenia than those with other blood groups. Statistically significant differences were found in the platelet count in the infectious period in group B Rh– compared with others (analysis of variance; $P = 0.003$) (FIGURE 2).

Pregnant women who had postpartum haemorrhage had a statistically significant decrease in the platelet count in the second (Student's t-test; $P = 0.008$) and third trimesters (Student's t-test; $P < 0.001$). In the second trimester, they had on average 55.52 × 10^9/l (95% CI 25.42 to 85.63 × 10^9/l) and in the third trimester 93.43 × 10^9/l (95% CI 62.47 to 124.39 × 10^9/l) platelets.

No statistically significant differences were found in platelet counts for types of delivery or APGAR. No correlation was found between platelet counts and cord pH.

No correlation was found between platelet count and D-dimer or C-reactive protein. A weak statistically significant

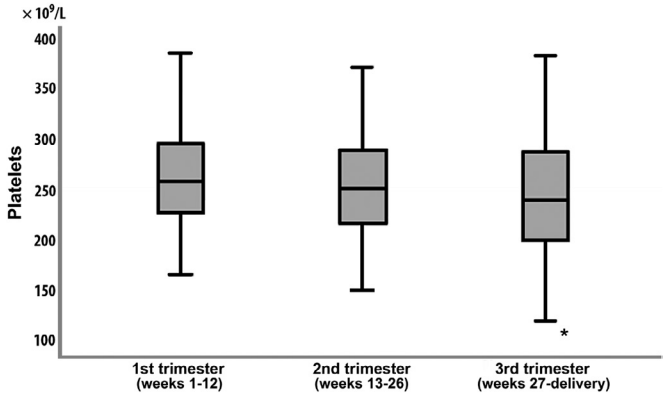

FIGURE 1 Box-and-whisker plot of platelet count in the three gestational trimesters. Paired student's t-test was used for comparisons between trimesters. *, statistical significance ($P = 0.009$).

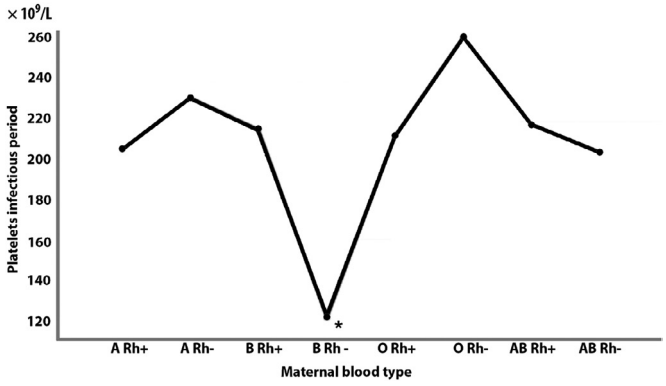

FIGURE 2 Maternal blood group and mean platelet count in the infectious period. Analysis of variance test was used for comparisons between groups. *, statistical significance (P = 0.003).

negative correlation was found between first-trimester platelet count and newborn APGAR (rho = –0.235; P = 0.024). A statistically significant negative correlation was also found between platelet count at delivery and maternal activated partial thromboplastin clotting time (rho = –0.348; P = 0.006).

An analysis of prothrombin time showed a statistically significant negative correlation with first trimester (rho = –0.256; P = 0.013), third trimester (rho = –0.312; P = 0.006) and delivery (rho = –0.352; P = 0.006) platelet counts.

No statistically significant correlation was found in platelet counts for heparin, non-steroidal anti-inflammatory drugs or antibiotics.

DISCUSSION

A greater number of studies are being published on the effect of SARS-CoV-2 infection in pregnancy. Understanding the repercussions helps us to establish appropriate measures to prevent and treat possible complications.

We found a significant increase in the age of women with thrombocytopaenia compared with those who did not have thrombocytopaenia. These data are consistent with the study by *Reese et al. (2018)*, in which the mean platelet count in young patients (age 15–19 years) was significantly higher than in women aged 20–44 years.

We were able to verify that pregnant women who smoke have a 6.54 times greater risk of presenting thrombocytopaenia than those who do not smoke. This result contradicts that found in previous studies in non-pregnant smoker patients (*Pedersen et al., 2019*; *Jayasuriya et al., 2020*), which report a significant increase in platelet count compared with non-smokers, which seems to suggest that COVID-19 infection may influence the results. This question could not be investigated as no studies were found on the relationship between thrombocytopaenia and smoking in pregnant women with and without COVID-19.

A recent publication in China (*Wu et al., 2020*) suggests that patients with blood group A have a greater susceptibility to SARS-CoV2 infection compared with patients with blood group O, who have less susceptibility. In contrast, a study conducted in Burriana, Castellón, Spain (*Domènech-Montoliu et al., 2021*), suggested no appreciable relationship between ABO group and the incidence of infection. This also indicates that participants in group B reported more symptoms and severity than other groups. Another study conducted in New York (*Anderson et al., 2021*) refuted any relationship between blood group and susceptibility to infection or severity of infection, given the prospective characteristics and the large sample size of this study.

Lippi et al. (2020) found a significant relationship between the severity of COVID-19 and thrombocytopaenia. Patients with thrombocytopaenia were five times more at risk of a more severe presentation. The percentage of patients with more severe disease in our study was similar to that reported by *Yan et al. (2020)*. In contrast, the percentage of asymptomatic pregnant women was almost three times higher in the present study. Only three patients had been hospitalized because of covid-19 pneumonia. In analysing gestational diabetes, we found no correlation with thrombocytopaenia, coinciding with the study by *Maconi et al. (2014)*, in which they also found no significant relationship between pregnant women with gestational diabetes and platelet count.

In women with gestational complications, pregnant women with thrombocytopaenia had a 16.182 times higher risk of preeclampsia than those without. Hypertensive states of pregnancy constitute one of the most important causes of gestation-related thrombocytopaenia. Although the causes of platelet decline are uncertain, platelet aggregation, which is increased in hypertensive patients, possibly due to vasospasm and microangiopathy, is thought to be involved (*Fogerty, 2018*). Although no evidence has been published, it would be interesting to analyse whether this relationship is bidirectional and thrombocytopaenia could develop subsequent to preeclampsia.

The platelet count in pregnant women varies in the different trimesters, with a gradual decrease as the pregnancy progresses (*Reese et al., 2018*; *Zitiello et al., 2020*). In agreement with these studies, we found a statistically significant decrease in platelets from the first to the third trimester. Furthermore, we found a significant negative correlation between gestational age at the time of infection and platelet count in the infectious period.

In the present study, 42.9% of the pregnant women were treated with low-molecular-weight heparins, of whom 7.6% suffered thrombocytopaenia; a value that does not seem to be caused by heparin, according to other studies mentioned above (*Reese et al., 2018*; *Zitiello et al., 2020*). Although heparin can reduce the number of platelets in an unintended way (heparin-induced thrombocytopaenia [HIT]), we did not find statistically significant relationship in platelet counts for heparin or the use of non-steroidal anti-inflammatory drugs or antibiotics, coinciding with the study by *Greer and Nelson-Piercy, (2005)*, which also did not associate any case of heparin-induced thrombocytopaenia. On the other hand, only one published study analysed the influence of blood group on the risk of HIT (*Ray et al., 2021*), finding

no significant differences between the different groups.

Haemogram tests showed that those with low haemoglobin had increased platelet count (39.53 × 10^9/l) compared with those with normal haemoglobin ranges. This may be due to iron deficiency, which can lead to a thrombocytosis ratio in iron-deficient patients of up to 33%, with a strong negative correlation with the severity of anemia (*Maryala and Vaddiparti, 2021*). Untreated iron-deficiency anaemia causes elevated levels of erythropoietin, which is postulated to cause an increase in platelets, in addition to erythrocytes, owing to the proliferation of bone marrow progenitor cells they have in common. This is probably caused by a similar amino acid sequence between erythropoietin and thrombopoietin (*Brissot et al., 2021*). We cannot affirm, however, that this is the cause, as blood iron values were not systematically collected from pregnant women. Other studies postulate that thrombocytopaenia may also occur in iron deficiency anaemias (*López and Macaya, 2013*; *Brissot et al., 2021*). The iron sequestration that can be seen in inflammatory conditions may be associated with thrombocytopaenia. This could justify the finding in our study of a statistically significant positive correlation between platelet count during the infectious period and haemoglobin during the same period.

Liang and Acharya (2020) have shown that, in addition to thrombocytopaenia, liver enzymes, LDH, D-dimer and C-reactive protein in patients infected with SARS-CoV2 are elevated. Pregnant women seem to present similar signs and symptoms, as well as altered laboratory values compared with the rest of the population. In the present study, we found a similar percentage of C-reactive protein determined in the infectious period and that of thrombocytopaenia and COVID-19 pneumonia.

We found a statistically significant negative correlation between platelet count and maternal activated partial thromboplastin clotting time. When prothrombin time was analysed, a statistically significant negative relationship was found with first trimester, third trimester and delivery platelets. This relationship clearly corresponds to the phases of haemostasis. In theory, although coagulation mechanisms are divided into different phases, they are all closely related, whereby activated platelets accelerate plasma coagulation, and coagulation activation products in turn induce platelet activation (*Alamin, 2021*; *Sierra et al., 2022*).

In the study by *Wang et al. (2017)*, gestational age at delivery was significantly lower in patients with hypertensive disorders and immune thrombocytopaenia compared with patients with pregnancy-associated thrombocytopaenia. We found no significant difference, however, between platelet counts and preterm delivery, nor an association between thrombocytopaenia and preterm delivery. Also, we observed no significant relationships between maternal age and preterm delivery, compared with the study by *Fuchs et al. (2018)*, in which the lowest risk of prematurity was in mothers aged between 30 and 34 years. Preterm delivery was mostly spontaneous in young women (aged 20–24 years), whereas, in women older than 40 years, it was most frequently iatrogenic.

Pregnant women who had postpartum haemorrhage had a statistically significant decrease in the platelet count in the second and third trimesters. These results are in agreement with several studies that found significant differences between lower platelet counts and postpartum haemorrhage (*Biguzzi et al., 2012*; *Carlson et al., 2017*; *van Dijk et al., 2021*).

The study by *Wei et al. (2021)* found that COVID-19 is associated with preeclampsia, stillbirth and preterm delivery compared with patients without COVID-19. In addition, they showed that symptomatic COVID-19 was associated with an increased risk of caesarean section and preterm delivery compared with asymptomatic COVID-19, with a greater association with preeclampsia, gestational diabetes, preterm delivery and low birth weight in the case of severe symptoms. We have not, however, been able to verify any of these points in our work as we did not observe statistically significant differences with these variables.

The median APGAR test in the study by *Yan et al. (2020)* at min 1 was 9, and at min 5 was 10. In the present study, no statistically significant relationships were found between platelet count and types of delivery or APGAR. Although not significant, the APGAR at 1 min of those with thrombocytopaenia was lower, although at 5 min, it recovered and at 10 min it was 10, which seems to suggest that COVID-19 infection could influence fetal wellbeing, although this point should be confirmed in further research.

In conclusion, the prevalence of thrombocytopaenia found in our study was similar to the prevalence described for the pregnant population without COVID-19 infection; therefore, we consider that infection is not a risk factor for platelet count. However, the main findings of the present work are that increased age, smoking and blood group B Rh– are risk factors for thrombocytopaenia in pregnant women with COVID-19 and that pregnant women with thrombocytopaenia have a 16-fold increased risk of preeclampsia. Finally, the results of our study seem to suggest that COVID-19 infection in pregnant women could influence fetal wellbeing, although this point should be confirmed in further research.

REFERENCES

Alamin, A.A. **The Role of Red Blood Cells in Hemostasis.** Seminars in thrombosis and hemostasis 2021; 47: 26–31. doi:10.1055/s-0040-1718889

Adelborg, K., Larsen, J.B., Hvas, A.M. **Disseminated intravascular coagulation: epidemiology, biomarkers, and management.** Br. J. Haematol. 2021 Mar; 192: 803–818. doi:10.1111/bjh.17172

American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. **Practice Bulletin No. 166: Thrombocytopaenia in Pregnancy.** Obstet. Gynecol. 2016; 128: e43–e53. doi:10.1097/AOG.0000000000001641

Anderson, J.L., May, H.T., Knight, S., Bair, T.L., Muhlestein, J.B., Knowlton, K.U., Horne, B.D. **Association of Sociodemographic Factors and Blood Group Type With Risk of COVID-19 in a US Population.** JAMA netw. open 2021; 4e217429. doi:10.1001/jamanetworkopen.2021.7429

Bauer, M.E., Chiware, R., Pancaro, C. **Neuraxial Procedures in COVID-19–Positive Parturients: A Review of Current Reports.** Anesth. Analg. 2020; 131: e22. doi:10.1213/ANE.0000000000004831

Biguzzi, E., Franchi, F., Ambrogi, F., Ibrahim, B., Bucciarelli, P., Acaia, B., Radaelli, T., Biganzoli, E., Mannucci, P.M. **Risk factors for postpartum hemorrhage in a cohort of 6011 Italian women.** Thromb. Res. 2012; 129: e1–e7. doi:10.1016/j.thromres.2011.09.010

Boushra, M.N., Koyfman, A., Long, B. **COVID-19 in pregnancy and the puerperium: A review for emergency physicians.** Am. J. Emerg. Med. 2021; 40: 193–198. doi:10.1016/j.ajem.2020.10.055

Brissot, E., Troadec, M.B., Loréal, O., Brissot, P. **Iron and platelets: A subtle, under-recognized relationship.** Am. J. Hematol. 2021; 96: 1008–1016. doi:10.1002/ajh.26189

Carlson, L.M., Dotters-Katz, S.K., Smid, M.C., Manuck, T.A. **How Low Is Too Low? Postpartum Hemorrhage Risk among Women with Thrombocytopaenia.** Am. J. Perinatol. 2017; 34: 1135–1141. doi:10.1055/s-0037-1604194

Chandra, S., Tripathi, A.K., Mishra, S., Amzarul, M., Vaish, A.K. **Physiological Changes in Hematological Parameters During Pregnancy.** Indian J. Hematol. Blood Transfus. 2021; 28: 144–146. doi:10.1007/s12288-012-0175-6

Ciobanu, A.M., Colibaba, S., Cimpoca, B., Peltecu, G., Panaitescu, A.M. **Thrombocytopaenia in Pregnancy.** Mædica 2016; 11: 55–60

Dashraath, P., Wong, J., Lim, M., Lim, L.M., Li, S., Biswas, A., Choolani, M., Mattar, C., Su, L.L. **Coronavirus disease 2019 (COVID-19) pandemic and pregnancy.** Am. J. Obstet. Gynecol. 2020; 222: 521–531. doi:10.1016/j.ajog.2020.03.021

Domènech-Montoliu, S., Puig-Barberà, J., Pac-Sa, M.R., Vidal-Utrillas, P., Latorre-Poveda, M., Rio-González, A.D., Ferrando-Rubert, S., Ferrer-Abad, G., Sánchez-Urbano, M., Aparisi-Esteve, L., Badenes-Marques, G., Cervera-Ferrer, B., Clerig-Arnau, U., Dols-Bernad, C., Fontal-Carcel, M., Gomez-Lanas, L., Jovani-Sales, D., León-Domingo, M.C., Llopico-Vilanova, M.D., Moros-Blasco, M., Notari-Rodríguez, C., Ruíz-Puig, R., Valls-López, S., Arnedo-Pena, A. **ABO Blood Groups and the Incidence of Complications in COVID-19 Patients: A Population-Based Prospective Cohort Study.** Int. J. Environ. Res. Public Health 2021; 18: 10039. doi:10.3390/ijerph181910039

Fogerty, A.E. **Thrombocytopaenia in Pregnancy: Mechanisms and Management.** Transfus. Med. Rev. 2018; 32: 225–229. doi:10.1016/j.tmrv.2018.08.004

Fuchs, F., Monet, B., Ducruet, T., Chaillet, N., Audibert, F. **Effect of maternal age on the risk of preterm birth: A large cohort study.** PLoS ONE 2018; 13e0191002. doi:10.1371/journal.pone.0191002

Gorbalenya, A.E., Baker, S.C., Baric, R.S., de Groot, R.J., Drosten, C., Gulyaeva, A.A., Haagmans, B.L., Lauber, C., Leontovich, A.M., Neuman, B.W., Penzar, D., Perlman, S., Poon, L.L.M., Samborskiy, D.V., Sidorov, I.A., Sola, I., Ziebuhr, J. **Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2.** Nat. Microbiol. 2020; 5: 536–544. doi:10.1038/s41564-020-0695-z

Greer, I.A., Nelson-Piercy, C. **Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy.** Blood 2005; 106: 401–407. doi:10.1182/blood-2005-02-0626

Guan, W.J., Ni, Z.Y., Hu, Y., Liang, W.H., Ou, C.Q., He, J.X., Liu, L., Shan, H., Lei, C.L., Hui, D.S.C., Du, B., Li, L.J., Zeng, G., Yuen, K.Y., Chen, R.C., Tang, C.L., Wang, T., Chen, P.Y., Xiang, J., Li, S.Y., Wang, J.L., Liang, Z.J., Peng, Y.X., Wei, L., Liu, Y., Hu, Y.H., Peng, P., Wang, J.M., Liu, J.Y., Chen, Z., Li, G., Zheng, Z.J., Qiu, S.Q., Luo, J., Ye, C.J., Zhu, S.Y., Zhong, N.S. **China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China.** N. Engl. J. Med. 2020; 382: 1708–1720. doi:10.1056/NEJMoa2002032

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., Gao, H., Guo, L., Xie, J., Wang, G., Jiang, R., Gao, Z., Jin, Q., Wang, J., Cao, B. **Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.** The Lancet 2020; 395: 497–506. doi:10.1016/S0140-6736(20)30183-5

Jayasuriya, N.A., Kjaergaard, A.D., Pedersen, K.M., Sorensen, A.L., Bak, M., Larsen, M.K., Nordestgaard, B.G., Bojesen, S.E., Çolak, Y., Skov, V., Kjaer, L., Tolstrup, J.S., Hasselbalch, H.C., Ellervik, C. **Smoking, blood cells and myeloproliferative neoplasms: meta-analysis and Mendelian randomization of 2o3 million people.** Br. J. Haematol. 2020; 189: 323–334. doi:10.1111/bjh.16321

Kazma, J.M., van den Anker, J., Allegaert, K., Dallmann, A., Ahmadzia, H.K. **Anatomical and physiological alterations of pregnancy.** J. Pharmacokinet Pharmacodyn 2020; 47: 271–285. doi:10.1007/s10928-020-09677-1

Kim, J.H., Shrestha, N., Girshin, M. **Unexpected Severe Thrombocytopaenia in the COVID-19 Positive Parturient.** Anesth. Analg. 2020; 131: e116. doi:10.1213/ANE.0000000000004948

Le Gouez, A., Vivanti, A.J., Benhamou, D., Desconclois, C., Mercier, F.J. **Thrombocytopaenia in pregnant patients with mild COVID-19.** Int. J. Obstet. Anesth. 2020; 44: 13–15. doi:10.1016/j.ijoa.2020.05.010

Liang, H., Acharya, G. **Novel corona virus disease (COVID-19) in pregnancy: What clinical recommendations to follow?** Acta Obstet. Gynecol. Scand. 2020; 99: 439–442. doi:10.1111/aogs.13836

Lippi, G., Plebani, M, Henry, B.M. **Thrombocytopaenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis.** Clin. Chim. Acta 2020; 506: 145–148. doi:10.1016/j.cca.2020.03.022

López, A., Macaya, C. **Plaqueta: fisiología de la activación y la inhibición.** Rev. Esp. Cardiol. 2013; 13: 2–7. doi:10.1016/S1131-3587(13)70073-6

Maconi, M., Cardaropoli, S., Cenci, A.M. **Platelet Parameters in Healthy and Pathological Pregnancy.** J. Clin. Lab. Anal. 2014; 26: 41–44. doi:10.1002/jcla.20502

Maryala, S., Vaddiparti, A. **Reactive Thrombocytosis Related Cerebral Venous Thrombosis: A Rare Complication of Untreated Iron Deficiency Anemia.** Cureus 2021; 13: e19064. doi:10.7759/cureus.19064

Mertz, D., Kim, T.H., Johnstone, J., Lam, P.P., Science, M., Kuster, S.P., Fadel, S.A., Tran, D., Fernandez, E., Bhatnagar, N., Loeb, M. **Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis.** BMJ 2013; 347: f5061. doi:10.1136/bmj.f5061

Narang, K., Enninga, E.A.L., Gunaratne, M.D.S.K., Ibirogba, E.R., Trad, A.T.A., Elrefaei, A., Theiler, R.N., Ruano, R., Szymanski, L.M., Chakraborty, R., Garovic, V.D. **SARS-CoV-2 Infection and COVID-19 During Pregnancy: A Multidisciplinary Review.** Mayo Clin. Proc. 2020; 95: 1750–1765. doi:10.1016/j.mayocp.2020.05.011

Pedersen, K.M., Çolak, Y., Ellervik, C., Hasselbalch, H.C., Bojesen, S.E., Nordestgaard, B.G. **Smoking and Increased White and Red Blood Cells.** Arterioscler Thromb. Vasc. Biol. 2019; 39: 965–977. doi:10.1161/ATVBAHA.118.312338

Rasmussen, S.A., Smulian, J.C., Lednicky, J.A., Wen, T.S., Jamieson, D.J. **Coronavirus Disease 2019 (COVID-19) and pregnancy: what obstetricians need to know.** Am. J. Obstet. Gynecol. 2020; 222: 415. doi:10.1016/j.ajog.2020.02.017

Ray, J.G., Warkentin, T.E., Park, A.L. **Heparin induced thrombocytopaenia in relation to SARS-CoV-2 infection and ABO blood group.** Thromb. Res. 2021; 207: 62–65. doi:10.1016/j.thromres.2021.09.008

Reese, J.A., Peck, J.D., Deschamps, D.R., McIntosh, J.J., Knudtson, E.J., Terrell, D.R, Vesely, S.K., George, J.N. **Platelet Counts during Pregnancy.** N. Engl. J. Med. 2018; 379: 32–43. doi:10.1056/NEJMoa1802897

Shrivastava, S.R., Shrivastava, P.S. **Minimizing the risk of international spread of coronavirus disease 2019 (COVID-19) outbreak by targeting travelers.** J. Acute Dis. 2020; 9: 47. doi:10.4103/2221-6189.278654

Sierra, C., Moreno, M., García-Ruiz, J.C. **The physiology of hemostasis.** Blood coagulation & fibrinolysis: an international journal in haemostasis and thrombosis 2022; 33: S1–S2. doi:10.1097/MBC.0000000000001099

Tang, M.W., Nur, E., Biemond, B.J. **Immune thrombocytopaenia due to COVID-19 during pregnancy.** Am. J. Hematol. 2020; 95: E191–E192. doi:10.1002/ajh.25877

Van Dijk, W.E.M., Nijdam, J.S., Haitjema, S., de Groot, M.C.H., Huisman, A., Punt, M.C.,

Evers, A.C.C., Schutgens, R.E.G., Lely, A.T., van Galen, K.P.M. **Platelet count and indices as postpartum hemorrhage risk factors: a retrospective cohort study.** J. Thromb. Haemost. 2021; 19: 2873–2883. doi:10.1111/jth.15481

Wang, X., Xu, Y., Luo, W., Feng, H., Luo, Y., Wang, Y., Liao, H. **Thrombocytopaenia in pregnancy with different diagnoses.** Medicine (Baltimore) 2017; 96: e7561. doi:10.1097/MD.0000000000007561

Wax, R.S., Christian, M.D. **Practical recommendations for critical care and anesthesiology teams caring for novel coronavirus (2019-nCoV) patients.** Can. J. Anaesth. 2020; 67: 568–576. doi:10.1007/s12630-020-01591-x

Wei, S.Q., Bilodeau-Bertrand, M., Liu, S., Auger, N. **The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis.** CMAJ 2021; 193: E540–E548. doi:10.1503/cmaj.202604

WHO, 2019. Coronavirus disease (COVID-19) – [Internet]. May 13, 2019. [cited 2020 Oct 5]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/coronavirus-disease-covid-19

WHO, 2020. Naming the coronavirus disease (COVID-19) and the virus that causes it [Internet]. [cited 2020 Oct 5]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it

Wu, B.B., Gu, D.Z., Yu, J.N., Yang, J., Shen, W.Q. **Association between ABO blood groups and COVID-19 infection, severity and demise: A systematic review and meta-analysis.** Infect. Genet. Evol. 2020; 84104485. doi:10.1016/j.meegid.2020.104485

Xu, X.W., Wu, X.X., Jiang, X.G., Xu, K.J., Ying, L.J., Ma, C.L., Li, S.B., Wang, H.Y., Zhang, S., Gao, H.N., Sheng, J.F., Cai, H.L., Qiu, Y.Q., Li, L.J. **Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series.** BMJ 2020; 368: m606. doi:10.1136/bmj.m606

Yan, J., Guo, J., Fan, C., Juan, J., Yu, X., Li, J., Feng, L., Li, C., Chen, H., Qiao, Y., Lei, D., Wang, C., Xiong, G., Xiao, F., He, W., Pang, Q., Hu, X., Wang, S., Chen, D., Zhang, Y., Poon, L.C., Yang, H. **Coronavirus disease 2019 in pregnant women: a report based on 116 cases.** Am. J. Obstet. Gynecol. 2020; 223: 111.e1–111.e14. doi:10.1016/j.ajog.2020.04.014

Zhang, Y., Zeng, X., Jiao, Y., Li, Z., Liu, Q., Ye, J., Yang, M. **Mechanisms involved in the development of thrombocytopaenia in patients with COVID-19.** Thromb. Res. 2020; 193: 110–115. doi:10.1016/j.thromres.2020.06.008

Zitiello, A., Grant, G.E., Ben Ali, N., Feki, A. **Thrombocytopaenia in pregnancy: the importance of differential diagnosis during the COVID-19 pandemic.** J. Matern. Fetal. Neonatal. Med. 2020; 35: 2414–2416. doi:10.1080/14767058.2020.1786527

Received 16 June 2022; received in revised form 14 October 2022; accepted 1 November 2022.