

# Transient severe thrombocytopenia with SARS-Cov-2 (COVID-19) infection in pregnancy

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## Abstract

A 24-weeks pregnant woman in her 2<sup>nd</sup> pregnancy presented with mild COVID symptoms and new onset rapidly progressive severe thrombocytopenia with a nadir of  $20 \times 10^9/L$ . She did not have any bleeding manifestations and the platelet counts recovered over 3 days without the need of steroids or immunoglobulin treatment. COVID-19 infection may cause transient severe thrombocytopenia, and this has not been previously reported in second trimester of pregnancy. We speculate the cause to be immune mediated. Other causes for severe thrombocytopenia were excluded after comprehensive investigations. This raise concerns on thromboprophylaxis and anticoagulant use in early pregnancies infected with COVID-19. Assessing the platelet counts at least two occasions few days apart of an infected patient may be a safer approach if continuing anticoagulants

**Key words:** severe thrombocytopenia, COVID-19, SARS-Cov-2, pregnancy, immune thrombocytopenia (ITP)

## Introduction

Sri Lanka has seen increasing numbers of patients with corona virus disease 2019 (COVID-19), with the delta variant, contributing to the upsurge. Many pregnant women have been affected, and several maternal deaths reported, due to COVID-19 infection and its complications. We report a pregnant woman presenting at her 24<sup>th</sup>-week of gestation with mild COVID symptoms

and recent onset severe thrombocytopenia. There are only 6 reported cases with COVID-19 related thrombocytopenia in pregnancy with only one presentation resulting in severe thrombocytopenia. All the reported cases presented in their third trimester. We report one of the most comprehensively investigated cases of COVID related thrombocytopenia in pregnancy up to date and a review of previously reported cases and management dilemmas.

*Sri Lanka Journal of Obstetrics and Gynaecology* 2021; **43**: 322-325

DOI: <http://doi.org/10.4038/sljog.v43i4.8028>

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Received 1<sup>st</sup> September 2021

Accepted 24<sup>th</sup> January 2022



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## Case report

A previously healthy 29-year-old mother of one child presented at 24-weeks of gestation in her second pregnancy with fever, headache, and myalgia for 2 days duration. She had a positive COVID rapid antigen test on day 2 of the symptomatic illness. On admission her platelet count was  $60 \times 10^9/L$ . Within 24 hours of admission, her platelet count dropped to  $25 \times 10^9/L$ . Over the next 12 hours her counts dropped further with a nadir at  $20 \times 10^9/L$ . She had no bleeding manifestations. There were no significant changes in her white cell (WBC) counts or haemoglobin levels.

The blood picture done by two independent hematologists showed severe thrombocytopenia with large forms of platelets. There was a mild neutrophilia with a left shift. The haemoglobin was 12.8g/dl without evidence of red cell fragmentation. It was concluded that the cause may be either immune thrombocytopenia or viral induced.

She had no previous medical complications that could have resulted in thrombocytopenia. She had an uncomplicated pregnancy and vaginal delivery at term, six years ago, with the baby weighing 3680g. She underwent booking visit at 9 weeks of gestation for her current pregnancy and recorded a platelet count of  $300 \times 10^9/L$ . The pregnancy was uncomplicated until she developed symptoms of a mild covid infection. She did not have any difficulty in breathing, sore throat, or cervical lymphadenopathy and neither had any features of pre-eclampsia. Her blood pressure remained stable at 120/80mmHg with urine protein creatinine ratio (UPCR) at 0.36.

Her covid polymerase chain reaction test was positive with a cycle threshold value of 22. During this period, she underwent several investigations aimed at excluding other causes of thrombocytopenia. On admission she had a CRP of 17.3mg/l which reduced to 5.7mg/l over the next two days (normal range 0-6). Her other inflammatory markers namely serum procalcitonin 0.023ng/ml and serum ferritin 24.16ng/ml were within the normal range. The D-dimer was 0.471mg/l (normal < 0.5). Her liver and renal profile tests were within normal limits (AST-14u/l, ALT-19u/l, Serum bilirubin-0.2mg/dl, PT/INR-1.07, APTT-27.9sec, Serum creatinine-0.54mg/dl). Her blood culture was negative. She was negative for acute dengue infection with both NS1 antigen and IgM antibodies absent in her serum. She also had normal hepatitis serology and ANA levels. Her chest x-ray did not show radiological evidence of

lung injury. Ultrasound revealed normal liver and spleen architectures. The 2D echocardiography was also normal.

Since there were no bleeding manifestations and she was clinically well, the patient was closely followed up with six hourly full blood counts. Steroids were considered but was not administered. Her platelet counts started to rise on day two of admission. The rise was rapid within the next 3 days with the platelet counts resuming normal levels. Both the patient and her fetus were well on discharge for home quarantine on day 8.

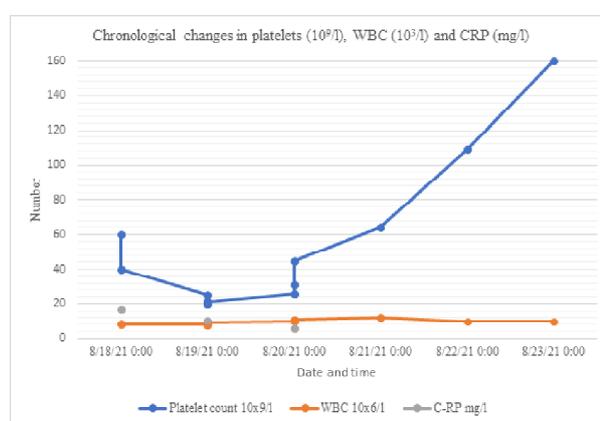


Figure 1. Chronological changes in platelets ( $10^9/l$ ), WBC ( $10^3/l$ ) and CRP (mg/l).

## Discussion

There were 6 reported cases of COVID-19 related thrombocytopenia in pregnancy since the onset of Coronavirus disease (COVID-19) pandemic. Mosses et al described platelet count of  $8 \times 10^9/L$  in a 36-year-old woman at 38-weeks of gestation with active systemic lupus erythematosus<sup>1</sup>. Aminimoghaddam et al reported a patient addicted to heroin with thrombocytopenia with a diagnosis of thrombotic thrombocytopenic purpura (TTP) at 29 weeks of gestation<sup>2</sup>. Both these cases had several risk factors for thrombocytopenia and therefore, COVID-19 could have been an incidental finding. The other reported COVID-19 pregnancies had the following features. 40-weeks gestation with a platelet count of  $94 \times 10^9/L$ , 31-weeks gestation with a platelet count of  $79 \times 10^9/L$ , 37-weeks gestation with a platelet count of  $40 \times 10^9/L$ , 29-weeks gestation with a platelet count of  $24 \times 10^9/L$  and 41-weeks gestation with platelet count reaching  $16 \times 10^9/L$ <sup>3,4,5</sup>.

Tang et al reported a patient at 41-weeks gestation with a starting platelet count of  $98 \times 10^9/L$  with a platelet nadir of  $16 \times 10^9/L$ . Since she needed delivery, the platelets were corrected with intravenous immunoglobulin (IVIg) and transfusion. Her platelet counts normalized over 3 weeks. Direct monoclonal antibody immobilization of platelet antigens (MAIPA) revealed platelet auto-antibodies against glycoprotein V and a diagnosis of ITP was made. The neonate also had platelets reaching  $41 \times 10^9/L$  on day 5. It was also reported that the patient had a sudden drop in saturation with ground glass appearance in chest x-ray<sup>5</sup>.

Kim et al reported a 29-weeks pregnancy who had an emergency delivery under regional anaesthesia. She presented with one-day history of fever and an initial platelet count of  $212 \times 10^9/L$ . Following delivery an incidentally detected platelet count of  $24 \times 10^9/L$ , led to correction of platelets with transfusion in anticipation of bleeding manifestations<sup>4</sup>. She had a rapid recovery of platelets to  $145 \times 10^9/L$  over the next 2 days. This case shows similar features to our patient with a rapid drop and recovery of platelet counts with mild COVID-19. However, other causes for low platelets were not investigated in this case

Our patient had thorough investigations to look for a cause of severe isolated thrombocytopenia. The patient did not have any features of pre-eclampsia. The liver and the renal function tests were within normal ranges with the blood picture not showing any evidence of hemolysis. Therefore, HELLP syndrome, TTP and HUS were unlikely. The serology confirmed no evidence of acute dengue infection in this patient. She was not on any drugs such as heparin, quinine, and penicillin which could cause thrombocytopenia. COVID vaccination had been described related to thrombocytopenia secondary to thrombosis. However, our patient did not have COVID vaccination.

Gestational thrombocytopenia (GTP) is a milder form of low platelets with the onset after the mid second trimester. Generally, the platelet counts are more than  $70 \times 10^9/L$  and rarely progresses below  $50 \times 10^9/L$  making it an unlikely cause in this patient<sup>6</sup>. Immune thrombocytopenia (ITP) is defined by a platelet count less than  $100 \times 10^9/L$ . An isolated thrombocytopenia without exposure to implicating drugs and splenomegaly and are suggestive of ITP<sup>7</sup>. Diagnosis of ITP is made either by excluding other disorders or on response to ITP-directed therapy<sup>6</sup>. ITP had been described following several viral infections including

Hepatitis B/C (HBV/HCV), Varicella zoster (VZV), Human immunodeficiency (HIV), Zika, Epstein-Barr (EBV), Parvovirus B19, cytomegalovirus (CMV) and SARS-Cov-2. In a systematic review of COVID-19 triggering ITP, Battacharjee investigated 45 reported cases including one pregnancy and 2 children. ITP in these patients occurred after clinical recovery from COVID-19<sup>8</sup>. Our patient had a rapid drop and a steep rise of platelet count over the course of 5 days which is uncommon in immune thrombocytopenia where usually recovery is prolonged and requires IVIg or steroids.

Possible mechanisms for thrombocytopenia following COVID-19 infection include suppression of bone marrow platelet production or circulating platelets destruction by lung injury or immune activation<sup>9</sup>. It is speculated that SARS-CoV-2 can infect bone marrow cells and inhibit hematopoiesis<sup>10</sup>. However, our patient had high CT values suggestive of lower number of viral particles in the blood stream. Therefore, this mechanism is less likely. Secondary hemophagocytic lymphohistiocytosis describes blood cell destruction caused by excessive proliferation and activation of mononuclear macrophage system, due to release of inflammatory cytokines resulting in a cytokine storm. This disease has a rapid progression with high mortality with the patient being unwell with high inflammatory markers specially serum ferritin which was not seen in our patient<sup>10</sup>.

Peripheral platelet destruction can be hypothesized by activation of platelets and microthrombi formation due to damaged lung tissues and pulmonary endothelial cells within the lungs. Usually, such patients will have x-ray changes with elevated d-dimer levels and impaired coagulation times, which was not seen in our case. The other hypothesis is that COVID-19 may increase production of autoantibodies and immune complexes, resulting in specific destruction of platelets by the immune system through molecular mimicry<sup>9</sup>. We speculate this may be the possible explanation in our case with the main mechanism likely to be immune mediated.

Pregnant women with COVID-19 are potentially exposed to an increased risk of thrombosis due to an intravascular inflammation, caused by the viral infection. Given the higher background risk of thrombosis in pregnancy, the need of prophylactic anticoagulation therapy in hospital admissions due to COVID-19 is recommended<sup>11</sup>. However, this would be inappropriate

in severe thrombocytopenia. With increasing numbers of pregnancies affected by COVID-19 more patients with early pregnancies are given home based care. This raise concerns in patients continuing aspirin for prophylaxis of pre-eclampsia. We suggest assessing the platelet count at least on two occasions, a few days apart before deciding to prophylactically continue antiplatelet or anticoagulant therapy.

### Author declarations

**Author contributions:** AJ, HS and SW contributed to the patient management. IP, HS did the data collection. IP and AJ developed the case presentation, IP, AJ, HS, SW contributed in editing, revisions and developing the final draft of the case presentation.

**Ethical considerations:** Informed written consent was obtained from the patient. Identifiable patient details or images are not mentioned in the case report.

### Acknowledgment

We acknowledge all the clinical and laboratory staff who had contributed to management of this patient.

### Abbreviations

HELLP – Haemolysis, elevated liver enzymes and low platelets

HUS – Haemolytic ureamic syndrome

TTP – Thrombotic thrombocytopenic purpura

GTP – Gestational thrombocytopenia

ITP – Immune thrombocytopenia

C-RP – C reactive protein

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