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Severe course of COVID-19 in pregnant woman and newborn's alloimmune thrombocytopenia — case study and review of the literature

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ABSTRACT

So far, little is known about the impact of the coronavirus disease 2019 (COVID-19) on pregnancy and data is often inconsistent. Even less information has been published on the management of severe courses of COVID-19 in pregnant women. By writing this article, we aim to share our experience in the treatment of pregnant woman critically ill with COVID-19 and newborn's condition, fetal and neonatal alloimmune thrombocytopenia (FNAIT), as well as literature review of this disease. After admission, the woman's respiratory status rapidly worsened, requiring administration of oxygen and in the end ECMO therapy. At the 9th day of ECMO support, and 28 weeks 3 days of gestation, due to mother's prognosis and increased feto-placental vascular resistance a decision of Caesarean section was taken. The neonate required intensive care not only due to extreme prematurity but coagulation disorder, alloimmune thrombocytopenia, which we diagnosed a few weeks after delivery.

Key words: pregnancy; COVID-19; ECMO; FNAIT

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by WHO on March 11, 2020. Pregnant women are particularly affected, but little is known about the impact of the coronavirus disease 2019 (COVID-19) on pregnancy and vice versa. The rate of preterm birth incidence in SARS-CoV-2 positive patients is 20% reported by Chen et al. [1] (out of 118 pregnancies), 17% by Allotey et al. [2] and 18.1% by Szczygiol et al. [3] Although current evidence suggest that development of severe COVID-19 in neonates is rare, in some cases there is necessity of NICU admission estimated in studies to 21.4% [3], 23% [4], 25% [2].

CASE PRESENTATION

A 36-year-old gravida-4 para-4 Iraqi woman with obesity presented at 26 weeks 4 days of gestation with cough, shortness of breath, and abdominal and chest pain. A nasopharyngeal reverse-transcript polymerase chain reaction (RT-PCR) swab returned positive for acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

At admission she was respiratory efficient and fetal status was reassuring. Ultrasound demonstrated the live fetus size was consistent with estimated dates. During the next few days, the patient's respiratory status rapidly worsened, requiring administration of oxygen therapy and subsequently high-flow nasal canula. The patient was placed on steroids, heparin, and broad-spectrum antibiotics.

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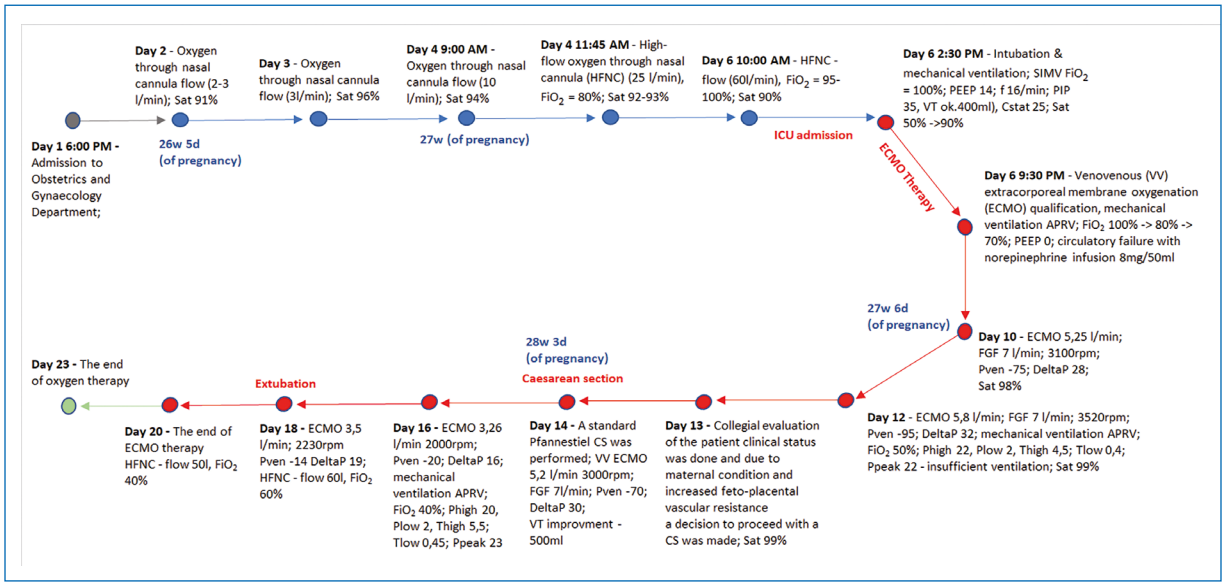

Figure 1. The course of COVID-19 in 36-year-old Gravida-4 Para-4 Iraqi woman; SIMV — synchronized intermittent mandatory ventilation FGF — fresh gas flow; PEEP — positive end-expiratory pressure; PIP — peak inspiratory pressure; f — frequency; ICU — intensive care unit; AF — atrial fibrillation; Pven — Venous pressure; VT — tidal volume; DeltaP — membrane pressure drop

A computed tomography (CT) scan of both lungs revealed areas of frosted glass shadow involving about 20% of the area of the lungs. Figure 1 summarises the course of the disease during this period.

On day six, due to the patient's critical acute respiratory distress syndrome (ARDS) status, intubation and ICU admission were needed. Considering a worsening hypoxia on maximal ventilatory support, venovenous (VV) extracorporeal membrane oxygenation (ECMO) was promptly instituted [5]. Since the case was extremely premature and observation of fetal wellbeing, it was decided that pregnancy should be continued. Close fetal surveillance was maintained by daily ultrasound with Doppler measurements and bidaily CTG traces. The absence of any variability in the CTG traces, accompanied by normal doppler findings, fetal movements, growth status, and amniotic fluid levels were all observed and linked to the patient's paralysis and sedation.

On the ninth day of ECMO support, and 28 weeks 3 days of gestation, a collegial evaluation of the patient's clinical status was undertaken, and due to the mother's condition and increased feto-placental vascular resistance we decided to proceed with a caesarean section. A standard procedure was performed uneventfully after a four-hour suspension of heparin infusion. A male neonate was delivered with Apgar scores of 2, 3, 3 and 4 (at 1, 3, 5, and 10 minutes of life, respectively), and a birth weight of 1.340 g. Table 1 shows the neonate's characteristics, vital signs, and laboratory results for the period of his hospital stay.

Despite an intraperitoneal bleeding diagnosed at postoperative Day 1 and consequent interventional reoperation, the mother's recovery was spectacular: after only 14 days of ICU therapy, and six days following delivery, the ECMO therapy was terminated. The patient was discharged to her home on day 29 in a good condition, with no oxygen requirement.

Regarding the neonate's post-delivery condition, cardiopulmonary resuscitation with chest compressions, and endotracheal intubation with mechanical ventilation were promptly instituted immediately after delivery due to progressive cardiorespiratory failure. Except for typical features of prematurity, physical examination revealed generalised soft tissue swelling, hypotonia, and decreased reflex irritability. Ultrasound was performed on the brain and abdomen on the third day of life and magnetic resonance imaging (MRI) on the 14th day of life. The ultrasound scans are shown in Figures 2 and 3.

Due to coagulation disorders in the course of SARS--CoV-2 reported after delivery in newborns, the coagulation parameters were monitored, despite the fact that no signs of hemorrhagic diathesis on physical examination. The infant's clinical laboratory results showed many disorders in coagulation results (Tab. 2, Fig. 4) and on the fourth day of life he developed mild thrombocytopenia. The most common causes of thrombocytopenia in preterm infants are pregnancy-induced hypertension (PIH), intrauterine growth restriction, preeclampsia, and HELLP syndrome [10]. On the other hand, thrombocytopenia in preterm infants that develops after 72 hours is most likely due to sepsis or necrotizing enterocolitis. We excluded all this disorders and after ultrasound findings decided to expand our research. Platelet genotyping and platelet

Table 1. Patient characteristics, vital signs, and laboratory results

Patient characteristics							
Gestational age	28 weeks						
Gender	Male						
APGAR (1, 3, 5 & 10 minutes of life)	2, 3, 3, 4						
Weight	1340 g (81 pc)						
SARS-CoV-2 (PCR)	Not detected						
Vital signs							
Heart rate	60 bpm						
Saturation	50–60%						
NIBP mean blood preasure	47 mmHg						
Temperature (rectal)	36.7°C						
Laboratory results							
Day of examination/ /measure	Hemoglobin [g/dL] (15.0–24.0)	White blood cells [1000/µL] (9.40–19.50)	Neutrophils [%] (40.0–68.0)	Lymphocytes [%] (19.0–48.0)	Platelets [1000/µL] (150–400)	Red blood cells [1000/µL] (4.00–6.60)	CRP [mg/L] (< 0.6)
Day 1	14.6	8.36	15.0	68.8	220	3.77	1.0
Day 2	7.6	11.41	48.5	28.6	141	2.89	–
Day 4	14.4	5.79	50.8	26.1	77	4.48	–
Day 13	11.2	13.88	37.3	28.4	364	3.55	1.9
On discharge	13.0	9.64	16.1	70.1	452	4.44	0.2

NIBP — noninvasive blood pressure; CRP — C reactive protein

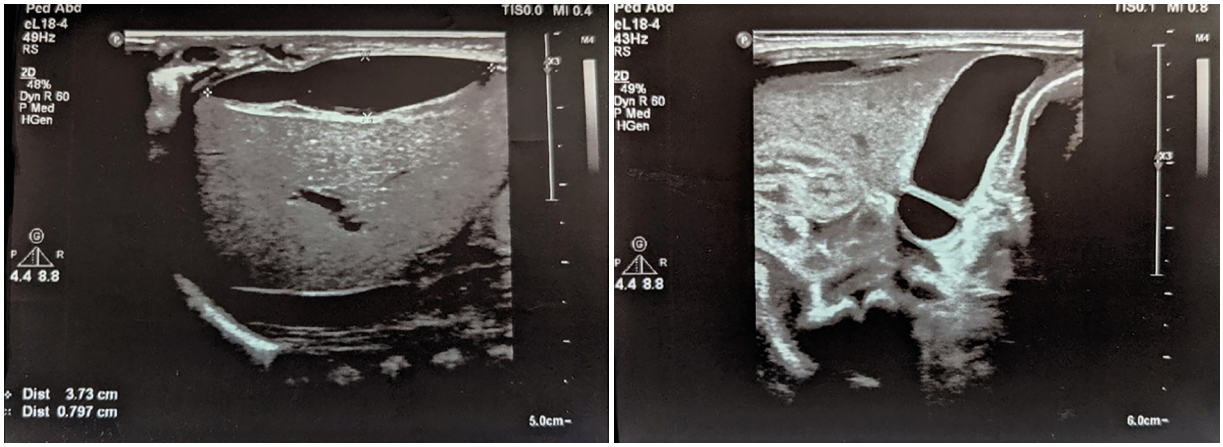

Figure 2. Abdominal ultrasound (3rd day of life) — subcapsular liver hematoma

antibody screening were performed, showing total HPA-3 system mismatch between mother (HPA-3A) and her son (HPA-3A/3B), with anti-HPA-3b antibodies in the mother's serum. This finding clearly confirmed the diagnosis of alloimmune thrombocytopenia.

The newborn was extubated on day six after delivery and after that he required nasal CPAP. At present, the child is in good general condition, with an efficient respiratory and circulatory system, tolerating oral intake. At that time, considering the young age of the baby and sedation which mother received, it was difficult to perform an appropriate neurological evaluation and express a definite prognosis. Although it is clear that the child is going to have major neurological impairment, a follow-up is ongoing.

DISCUSSION

Considering this case, it is extremely challenging to understand the possible implications of ECMO itself for the

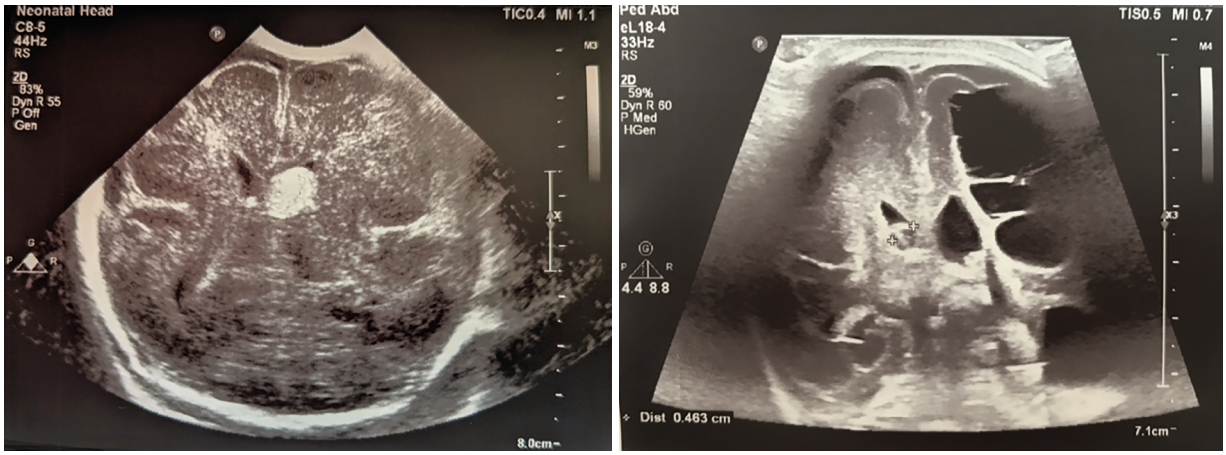

Figure 3. Brain ultrasound (3rd day of life) — intraventricular haemorrhage grade II, disseminated hyperechogenic lesions of both sides, subdural haemorrhage on the left side and widening of the cerebral space on the right side

Table 2. Coagulation parameters

Coagulation parameters				
Day of examination/measure	APTT [sec.] (25.4–36.9)	D–dimer [ug/l FEU] (445–1200)	Platelets [1000/μL] (150–400)	INR (0.90–1.20)
Day 1	47.0	11 941	220	1.93
Day 2	33.3	–	141/107	2.54
Day 4	27.4	–	77	1.09
Day 6	–	–	–	0.89
Day 13	–	4 947	364	–
Day 18	–	–	526	–
On discharge	–	–	452	–

APTT — activated partial thromboplastin time; INR —international normalized ratio

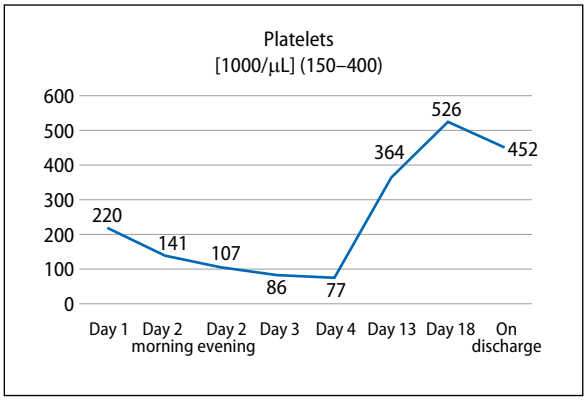

Figure 4. Coagulation parameters (platelets) — change over time

fetus and the newborn. It illustrates clearly that COVID-19 in pregnant patients may have a rapid and unpredictable course. There is limited data on ECMO therapy in pregnant COVID-19 women and therefore management is challenging [6, 7]. In most of the available data, emergency deliveries were performed before the initiation of ECMO.

A case series published by Barrantes et al. [6], shows only two cases where delivery was performed post-ECMO. In our case, the decision to delay the delivery was grounded on the mother's condition, which was worsening rapidly and therefore the initiation of ECMO could not be delayed and performing the surgery at that time could have even worsened the prognosis. We scheduled caesarean delivery on the 9th day of ECMO, when the mother's condition was stable enough for surgery, however the woman did not show any signs of a prompt recovery. The decision at that time was made to improve the prognosis of the mother, which was in fact achieved, as further recovery was rapid post-operatively.

When it comes to the newborn, the boy's condition was unexpectedly worsening not only due to extreme prematurity but also because of fetal and neonatal alloimmune thrombocytopenia (FNAIT), caused by an HPA-3a type antigen, which we discovered a couple of weeks post-delivery. Fetal and neonatal alloimmune thrombocytopenia is the most frequent cause of severe thrombocytopenia (defined as a platelet count $\leq 50 \times 10^9$/L) in term-born infants and the most common cause of intracranial haemorrhage (ICH) [8, 9].

Fetal and neonatal alloimmune thrombocytopenia is caused by the production of maternal alloantibodies against the paternally derived, fetal human platelet antigens (HPAs). In Caucasians, the most frequently involved antigen is the human platelet antigen -1a (75–80%) [9]. Other commonly involved antigens are human platelet antigen-5b, anti-human platelet antigen-15b, and human platelet antigen-3a (15%), but other rare antigens can also be involved (< 5%). The incidence of fetal and neonatal alloimmune thrombocytopenia has been estimated at 1/800 to 1/1000 live births [10]. Clinical consequences can vary from an asymptomatic thrombocytopenia to minor skin haemorrhage, such as haematoma or petechiae, or ultimately severe internal organ and intracranial haemorrhage (ICH) with long term neurologic complications. Approximately 10–25% of children with severe thrombocytopenia caused by FNAIT develop an ICH [11]. In contrast to maternal immunisation against fetal red cell antigens, it is common for immunisation against platelet alloantigens to occur during a first pregnancy and for a firstborn infant to be affected by FNAIT. As FNAIT is a rare condition and not often recognised by clinicians, in most cases it is diagnosed after birth of a child with symptoms of thrombocytopenia or CNS haemorrhage. The most reliable predictor for the occurrence of severe bleeding complications so far is the occurrence of an ICH in siblings [12]. Moreover, sisters of HPA-1a negative women should be tested and pregnancies with ultrasounds findings such as ICH or hydrocephalus [13]. Screening and timely treatment is the only way to prevent severe complications. Maternal immunoglobulin administration is first line treatment according to the most recent international guideline on clinical management strategies of FNAIT [14]. The use of corticosteroids is also reported but in most studies, there was no evidence of beneficial effect [15]. Another future therapeutic option might be a neonatal Fc receptor blocker that can inhibit the transportation of alloantibodies over the placenta [16, 17].

CONCLUSIONS

The above case study shows how unpredictable and life-threatening the course of COVID-19 in pregnant women can be. Currently, prophylaxis is the only method for minimising severe consequences of COVID-19, both in the mother and the baby. The other conclusion is that FNAIT is an underdiagnosed condition. The detection of FNAIT remains low and creates a challenge for clinicians especially at an early stage. HPA-1a testing is the best method for diagnosing pregnancies at risk. The introduction of general screening programs for FNAIT should be under consideration.

Article informations and declarations

Conflict of interest

All authors declare no conflict of interest.

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