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Case Report

Sars-Cov2 Induced Coagulopathy during Pregnancy: A Case Report of Disseminated Intravascular Coagulation in a Pregnancy with Mild Covid-19

Mokhamad Zhaffal MD [1], Brenda McLaughlin MD [2], Anastasia Salame MD *[3]

1. *Obstetrics and Gynecology department, Kanad Hospital, Adjunct Assistant Professor in the Department of Obstetrics and Gynecology of Medicine and Health Sciences, UAE University, Al Ain -UAE.*

2. *Obstetrics and Gynecology department, Kanad Hospital, Chief medical officer, Al Ain- UAE.*

3. *Reproductive Endocrinology and Infertility department, ART Fertility Center, Al Ain, UAE.*

*__Correspondence to:__ Anastasia Salame, M.D. Reproductive Endocrinology and Infertility department, ART Fertility Center, Al Ain, United Arab Emirates.

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Abbreviation

Abbreviation	Meaning
ARDS	Acute respiratory distress syndrome
CTG	Cardiotocography
DIC	Disseminated intravascular coagulation
IUFD	Intra uterine fetal demise
IVF	In vitro fertilization
LFT	Liver function tests
PPH	Post-partum hemorrhage

Table 1: list of the abbreviations used in the manuscript.

Keywords: Covid-19, Pregnancy, Coagulopathy, Disseminated intravascular coagulation, Hemorrhage, Postpartum.

Introduction

Covid -19 has become the latest pandemic that humanity had and still is facing. Due to unknown mechanisms and unorthodox course of illness, COVID-19 infected patients present with various unprecedented complications. Coagulopathies are of the most feared as they carry a high mortality rate. Most of the published data agree on the high incidence of deep venous thrombosis highlighting the fact that the pathophysiology of COVID-19 associated coagulopathy is complex and remains to be fully understood [1]. After extensive research, it has been found that the coronavirus can infect endothelial cells via the ACE2 which acts as a receptor for the SARS-CoV-2. The endothelial binding of the coronavirus limits the ACE2 ability to play its role in maintaining the coagulation factor balance with the vascular system. This leads to the exacerbation of the cellular damage with concomitant downregulation of the protein C anti-coagulation system, hence the frequent occurrence of thrombotic events [2].

This is reflected with the markedly elevated levels of D-dimer and mild decrease in median platelet counts with normal PT values [3]. Consumptive coagulopathy on the other hand is not a frequent complication, for example, disseminated intravascular coagulation (DIC) occur in less than 1% of critically ill patients [4].

Pregnancy, however, is associated with more frequent complications as there is a growing body of evidence that COVID infection during pregnancies are associated with adverse maternal outcomes. Pregnancy associated cardiovascular changes, immunosuppressed state and the pre-existing medical comorbidities predispose pregnant patients to complications during the course of COVID-19 infection. Studies have showed that around 3% of COVID- 19 pregnancies end up associated with severe maternal morbidity such as maternal pneumonia, sepsis, disseminated intravascular coagulopathy, preterm birth, and maternal death especially in the setting of severe COVID infections [5], [6]. Given that pregnant women are at a physiologic immunocompromised state and are at a higher risk of COVID-19 complications, more light should be shed on the pathophysiology as well as treatment course in infected pregnant patients. This is due to the presence of atypical cases in daily practice.

We present a case report of DIC in a 3rd trimester pregnant patient diagnosed with COVID- 19 of mild severity without any other risk factor. A literature review was done to highlight possible antenatal follow up strategies for COVID-19 infected patients. Treatment approaches of such cases to avoid maternal and neonatal morbidity and mortality were also suggested.

Case Report

In June 2021, a 33-year-old G1P0 female patient presented at 33+6 weeks of gestation to the respiratory urgent care clinic with COVID-19 infection, two episodes of minimal vaginal bleeding since the morning and a 2-day history of persistent high-grade fever. The patient's pregnancy was a product of in vitro fertilization (IVF) after 10 failed attempts. The patient was previously healthy with no surgical history. The patient was diagnosed with COVID-19 4 days prior to presentation, was found to have thrombocytopenia (95K) but discharged home since she was in a stable condition with a normal saturation of 97%. She was considered to have mild COVID-19 infection at that point.

Upon presentation, the initial assessment showed a febrile patient with a temperature of 38.40C but no respiratory distress (respiratory rate: 12 rpm, pulse: 85 bpm, blood pressure: 110/70 mmHg, saturation: 96%). No active vaginal bleeding was noted. However, cardiotocography (CTG) revealed regular contractions every 3-4 minutes with a category II tracing (fetal tachycardia and late decelerations less than 50% of the tracing). The pelvic exam showed a posterior thick closed cervix. A bedside obstetric ultrasound revealed no abnormalities. Chest X-ray revealed haziness at the right lower zone.

Intravenous hydration started with 1-liter lactated ringer and one gram of paracetamol given and blood tests were ordered. Two hours post presentation, the patient developed abdominal pain and the CTG revealed a category III tracing with recurrent late decelerations with each contraction. The patient was suspected of having placental abruption and emergency caesarean section was called. Blood tests revealed thrombocytopenia of 29000, prolonged INR and aPTT, elevated LDH at 535 U/L and increasing liver function test (LFT) (Table 2). As a result, two units of PRBCs, two units of FFP s and four units of platelets were prepared as the patient was being taken into the operating room. The Caesarean section was performed without any complication intra-operatively. No placental abruption was noted. A baby girl was delivered uneventfully 60 seconds after the cutting time with Apgar score of 8 and 10 at 1 and 5 minutes, respectively. The estimated blood loss intra-operatively was 450 ml and the patient received ten units of Oxytocin®, one gram of tranexamic acid and one dose of Carboprost tromethamine® prophylactically with a well contracted uterus. After the closure of the skin incision, the patient started having oral and vaginal bleeding. An obstetric code was declared, and massive transfusion protocol was applied as the patient was diagnosed with DIC. A Bakri balloon was inserted followed by placement of a vaginal pack. Bed side transabdominal ultrasound confirmed the proper placement of the balloon and the lack of any intra-abdominal bleeding. The patient received three doses of Carboprost tromethamine®, one gram of Tranexamic acid, 40 units of Oxytocin®, 800 micrograms of Misoprostol®, 5 units of PRBC's, 1 pool of platelets and 3 units of fresh frozen plasma. The patient was stabilized in our hospital with a total blood loss of 3000 ml at the end of the procedure. The patient was then transferred to a tertiary care center where uterine artery embolization was performed due to recurrence of vaginal bleeding. The procedure was uneventful after which no active bleeding or extravasation was seen. The patient was then transferred intubated into the ICU unit. In the ICU, Remdesivir, steroids (Prednisone) and Tazobactam were started to complete a course of 5 days. The patient was extubated after 24 hours. The patient was diagnosed with bilateral COVID induced pneumonia on day two post operatively and was transferred to the regular floor where she continued 3 more days of her treatment. She was discharged home in a stable condition on day six post operatively. It is worth mentioning that the patient's D Dimer increased to a maximum of 6.8 mg/dL while the fibrinogen remained relatively stable between 2-4 g/L. Table 2 summarizes the blood tests done for the patient during her COVID- 19 illness pre and post operatively. Unfortunately, the fibrinogen level is not available upon presentation. However, if we take into consideration that after correction the values ranged between 2.7 and 2.9 g/L, it would be safe to assume that it was below 2 g/L at the time of presentation and intra-operatively which makes the DIC score three as per Clark et al [7]. The pregnancy DIC score is presented in Table 3.

The baby was admitted to the NICU for prematurity, received supportive care and discharged home on day eight of life in a stable condition. The baby tested negative for COVID and had a smooth neonatal course.

The patient provided a written consent allowing the use of her data anonymously.

	4 days prior to presentation	**Upon presentation 17:52**	**Post op day zero, 01:23**	**Post op day 0, 03:36**	**Day 1 post op**	**3 days post op**	**4 days post op**	**6 days post op**	**10 days post op**
WbcK/uL	7.06	4.71	4.42	6.6				8.61	6.92
Hg g/dL	10.3	10.7	10.8	9.3	10.6			9.9	12.2
Hct %	32.6	33.8	35.10	26	29			29.9	38.3
Platel ets K/uL	95	29	29	28	85			205	378
Fibrinogen g/L				**2.97**	**2.77**	3.96		**3.58**	
D-Dimer mg/L	**1.07**			**6.8**	**0.57**	0.37			**1.16**
INR		**1.41**		**0.75**	**0.89**	0.95		**1.03**	
aPTT sec		**58.9**				31.5		**28.9**	
ALT U/L	**13.6**	**34.2**					70.6	**54.5**	
AST U/L	**18.6**	**75.1**				74.4			

Table 2 Blood tests done for the patient.

Discussion

1. Risk factors

Since the documentation of the first case of COVID-19 in December 2019, more than six hundred million people have been infected and more than 6.5 million deaths reported due to COVID-19 infection and related complications [8]. It has been noted so far that people suffering from chronic disease, have co-morbidities like diabetes, hypertension, malignancies, and obesity or are pregnant are at an increased risk of COVID related complications and death. Multiple reports showed that pregnant women tested positive for COVID-

19 more frequently even when only screening in comparison to non-pregnant patients. Reports show that asymptomatic infections in pregnant patients is 15-fold higher than in non-pregnant controls, while the rate of documented infections was 9% in pregnant patients in comparison to 5 % in age-controlled women. However, due to the substantial amount of missing data, the authors could not conclude that pregnancy per se predisposed patient to contracting COVID-19 [9]–[11]. Multiple data sources confirmed however that COVID-19 during pregnancy is associated with higher rates of complications, morbidities, and mortality. Admission to the ICU, mechanical ventilation, deep venous thrombosis events and death were found to be significantly higher in pregnant patients. The relative risk (RR) for ICU admission was found to be 3, for mechanical ventilation 2.9 and for death 1.7 respectively [11]. Data from United Kingdom's Obstetric Surveillance System and from the Surveillance for Emergency Threats to Mothers and Babies Network in the United States highlighted advanced age, Black race, obesity, chronic lung disease, hypertensive disease, pregestational diabetes and asthma as risk factors for more severe COVID-19 disease with a higher chance for admission [12], [13].

2. COVID-19 pregnancy related complications

Most of the studies pointed out that COVID infection does increase the rate of ante-natal complications. Furthermore, pregnant patients diagnosed with severe COVID-19 are at a higher risk of comorbidities when compared to asymptomatic patients. Multiple metanalyses showed that COVID positive status was associated with preeclampsia, preterm birth, gestational diabetes, low birthweight, cesarean sections and still birth especially in the setting of severe disease [14], [15]. COVID-19 has also been found to increase the risk of peripartum and postpartum bleeding tendencies. In a cohort study published by Epelboin et al in 2021, the odds ratio (OR) for peripartum hemorrhage and post-partum hemorrhage was 3.1 and 1.8 respectively [16]. This was supported by another study published by Hcini et al also in 2021 where the RR of having postpartum bleeding was 2 [17]. However, the risk of developing DIC was found to be extremely low and mainly related to the severity of COVID infection.

DIC has been described in only 0.7% to 1.3% of severe COVID cases during pregnancy [18], [19]. Vertical transmission from mother to neonate has been found to be extremely rare. This might be explained by the low placental concentration of ACE-2 receptors and TMPRSS2 receptors that are believed to function as ligands for the entry of ARS-CoV-2 into cells.

Breastfeeding was not found to predispose neonates to risks of infections especially when the mother was asymptomatic or practiced safety measures such as mask wearing and hand hygiene [20].

3. DIC in asymptomatic or mild cases

As already mentioned in section 2.2, DIC was found to be prevalent mainly in pregnant patients with severe COVID-19 infection. However, there are publications reporting DIC in patients with asymptomatic or mild COVID with no other obvious risk factors. Like our case, the common presenting symptom in these patients was decreased fetal movement with or without non-reassuring fetal heart tracing in the setting of late second to early 3rd trimester [21], [22]. Carpenter et al reviewed all the DIC cases in mild COVID infected patients (27 cases) submitted by the maternal fetal medicine specialists. As per Carpenter et al, the most common findings in these 27 patients were thrombocytopenia, hypofibrinogenemia (80% of cases) and decreased fetal movement. In 95% of cases, blood products were transfused and 2 patients required a peripartum hysterectomy. The incidence of intrauterine fetal demise (IUFD) was found to be 35% which is much higher than what was published earlier in pregnant COVID-19 patients (35 % versus 2.7%) [22]. Even though the frequency of DIC in such cases is believed to be extremely low, the extent of negative outcome and possible devastating consequences mandate a certain level of preparedness. This is of high importance especially in the setting of non-reassuring fetal heart tracing or decreased fetal movement as it was noted to be predictive or related to DIC in mild or asymptomatic COVID cases. The diagnosis of DIC in pregnant patients is based on a high index of suspicion and a scoring system suggested by Clark et al that was modified to fit pregnant patients. The score is the sum of the marks provided to each of the three blood tests that were found to be the most diagnostic: platelet count, fibrinogen level and prothrombin level [7]. The scoring system is presented in Table 3.

It is well known that placental abruption, IUFD, severe pre-eclampsia and amniotic embolism disrupt the proper placental function thus leading to DIC. In general, any placental injury would lead to the release of the coagulation cascade activating factors in large concentrations followed by exacerbated thrombin production and resultant DIC. In COVID patients, like the case presented in section 0, without a clear risk factor, the trigger of DIC remains unknown. One of the suspected culprits is thought to be SARS-CoV-2 placentitis. Multiple reports have documented placental pathologic changes in COVID infected patients including histiocytic intervillositis, perivillous fibrin deposition and necrosis [21]–[23]. It is worth mentioning that those findings are neither universal nor pathognomonic for COVID-19 pregnant patients or

the ones complicated by DIC. In fact, some COVID DIC cases with IUFD have a completely normal histopathological placenta report [22].

Blood test	Value	Score
Platelet count	≤100,000 per mm^3	1
fibrinogen	≤200 mg/L	1
prothrombin time	prolonged ≥3 seconds above theupper limit of normal	1
Score of 3 is consistent with DIC [7]		

Table 3 DIC diagnostic criteria cutoff values in pregnant patients

4. Treatment of at-risk cases:

The mainstream treatment for DIC is delivery, removing the culprit which is the placenta and correcting the coagulation profile via blood product transfusion with frequent monitoring.

However, it remains of crucial importance to prevent DIC especially knowing the unfavorable outcomes associated with the latter occurrence. Keeping in mind that there are no specific criteria for patient stratification, the treating physician should remain vigilant in the setting of 2nd and 3rd trimester pregnancy with COVID infection even with the absence of symptoms. Patients who state having decreased fetal movement even with mild COVID-19 infection are advised to have fibrinogen level, prothrombin time and a complete blood count to assess the platelet levels. Patients who are found to have thrombocytopenia, especially below 100,000 might be amenable for admission and close monitoring as they might be at risk of rapid deterioration and developing DIC. Delivery of those patients should be based on the maternal and fetal well-being to avoid any IUFD and possibly DIC [22].

Conclusion

DIC has been documented as a rare yet devastating complication in pregnant patients infected with SARS-CoV-2. Even in the setting of mild or asymptomatic disease, any pregnancy related complaint should be taken seriously and followed up closely.

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