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COVID19 and acute coagulopathy in pregnancy

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Key Points

1) We present the first reported cases of rapidly progressive coagulopathy, improving with delivery in maternal COVID19 infection in the 3rd trimester.

2) In COVID-19 pregnancies, APTT and fibrinogen testing, in addition to D-dimers, prothrombin time, and platelet count performed in all patients, may add diagnostic and risk-stratifying value.

Abstract

We present a putative link between maternal COVID19 infection in the peripartum period and rapid maternal deterioration with early organ dysfunction and coagulopathy. The current pandemic with SARS-CoV-2 has already resulted in high numbers of critically ill patients and deaths in the non-pregnant population, mainly due to respiratory failure. During viral outbreaks, pregnancy poses a uniquely increased risk to women due to changes to immune function, alongside physiological adaptive alterations, such as increased oxygen consumption and edema of the respiratory tract. The laboratory derangements may be reminiscent of HELLP syndrome, and thus knowledge of the COVID19 relationship is paramount for appropriate diagnosis and management. In addition to routine measurements of D-dimers, prothrombin time, and platelet count in all patients presenting with COVID19 as per ISTH guidance, monitoring of APTT and fibrinogen levels should be considered in pregnancy, as highlighted in this report. These investigations in SARS-CoV-2-positive pregnant women are vital, as their derangement may signal a more severe COVID19 infection, and may warrant pre-emptive admission and consideration of delivery to achieve maternal stabilization.

Introduction

The present COVID-19 pandemic due to SARS-CoV-2 novel coronavirus has resulted in high numbers of critically ill patients and deaths[1]. Emerging data on the maternal impact of COVID19 suggest that the clinical course is similar irrespective of pregnancy[2-4]. However, despite these data, our report of two pregnancies with COVID19-related, rapidly-progressive coagulopathy may warrant caution.

Methods

Case 1 (C1): 40-year-old gravida 2 para 1, followed at Mount Sinai Hospital, Toronto, Canada, with familial neutropenia diagnosed in infancy, with an uncomplicated course in adulthood. Pregnancy was complicated by gestational diabetes, neutropenia (0.1-0.3 x 10^9/L), and mild respiratory infections treated with antibiotics. She was commenced on G-CSF 4-weeks prior to admission and admitted at 35+3 weeks' gestation with cough and pyrexia. Normotensive, tachycardic (110-121 beats/minute), febrile (39°C), with normal oxygen saturation in room air. Fetal heart rate monitoring was unremarkable. Normal obstetrical ultrasound demonstrated a well-grown fetus. Piperacillin/tazobactam was commenced for febrile neutropenia, and filgrastim was 300mcg

continued (Table 1). SARS-CoV-2 was confirmed by PCR on a nasopharyngeal swab. The chest x-ray was normal. Over 48 hours, there was progressive thrombocytopenia, declining fibrinogen, and rising APTT with concomitant improvement in neutrophil count, responding to G-CSF (Table 1). Respiratory parameters were stable. There was collaboration of obstetric, haematologic, infectious disease and anesthesiologic teams in her care. Differential diagnoses included COVID19, sepsis with familial neutropenia masking superimposed bacterial infection, and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. The latter in the absence of hypertension, hemolysis, or proteinuria, was considered extremely unlikely. Mild transaminitis was ascribed to underlying infection (Table 1). Owing to concerns that progressive coagulopathy would preclude neuraxial anesthesia, and aiming to avoid general anesthesia (GA), she was delivered via repeat CS under spinal anesthetic on admission day 2. She sustained a postpartum hemorrhage (PPH) of 1.5L controlled with uterine artery ligation and B-Lynch compression, alongside uterotonics and blood products (tranexamic acid 2g, fibrinogen 4g, cryoprecipitate 10 units). LMWH prophylaxis was initiated 12 hours later. Coagulopathy improvement was noted on postoperative day (POD)2 (Table 1). Piperacillin/tazobactam was continued. Filgrastim was increased to 480mcg daily and discontinued on POD3. A healthy male infant was delivered, weighing 2.93kg (Apgars of 9 and 9 at 1 and 5 minutes). Breastfeeding was initiated with pediatric clearance. Mother and infant were discharged on POD4, with self-isolation instructions.

Case 2 (C2): 23-year-old gravida 1 para 0 admitted to a peripheral hospital at 35+2 weeks' gestation with cough and pyrexia (38.6°C). Nasopharyngeal swab demonstrated SARS-CoV-2. Thrombocytopenia, prolonged APTT, and transaminitis (Table 1) triggered transfer to Antoine Béclère hospital in Clamart, France. Medical history was remarkable for asthma and BMI 32. No evidence of hypertension/proteinuria. Following transfer, there was progressive deterioration in coagulation parameters (Table 1). A non-reassuring fetal heart rate coupled with progressive coagulopathy and transaminitis prompted emergency CS under GA. Fibrinogen 3g and tranexamic acid 1g were administered prior to delivery. A male infant was born at 35+5 weeks, weighing 2.54kg (Apgars of 4, 2, 7 at 1, 5 and 10 minutes). There was no excessive bleeding and. Coagulopathy resolved by POD1. Prophylactic LMWH administered on POD1. Respiratory symptoms remained stable, and she was discharged home on POD5.

Discussion

This is the first report describing COVID19-related acutely-progressive coagulopathy in the third trimester of pregnancy, the recovery of which appears to be hastened by delivery. Coagulopathy results from concurrent activation of the coagulation and fibrinolytic cascades, here likely triggered by sepsis, causing clotting factor consumption. Manifestations can be either thrombotic or hemorrhagic. Pregnancy adds further complexity, given its physiologically hypercoagulable state, with rising coagulation factors, including a fibrinogen and D-dimers increase to 50% above baseline by the third trimester[5].

While C1 had underlying familial neutropenia, and plausibly her relatively immunocompromised state contributed to the COVID19 course, chronic neutropenia is not a recognized cause of pregnancy-associated coagulopathy. A retrospective cohort study examining 38 pregnancies with chronic neutropenia syndromes, noted no coagulopathy cases[6].

Significantly elevated D-dimers were observed in both cases (17-fold upper normal range in pregnancy (UNLP) and 12-fold UNLP). Concerningly, recent reports position elevated D-dimers as a poor prognostic indicator in non-pregnant individuals. Huang et al. noted higher D-dimers in those requiring ICU admission vs. those who did not (median D-dimer 2.4 mg/L (0.6-14.4) vs. 0.5 mg/L (0.3-0.8); p=0.0042) [7]. Tang et al. observed higher D-dimers in non-survivors vs. survivors [2.12 ug/mL (range 0.8-5.3 ug/mL) vs. 0.6 ug/mL (0.4-1.3 ug/mL)][8]. Given the typical D-dimer rise during gestation[5], it remains unclear what D-dimer threshold would indicate unfavourable prognosis in pregnancy. The ISTH suggests that those with significant D-dimer elevation (arbitrarily defined as a 3-4 fold above ULN) be hospitalized even in the absence of other concerning symptoms[9].

Outside of pregnancy, anticoagulation of coagulopathic, septic patients improves outcomes[10]. ISTH established a scoring system to identify “sepsis-induced coagulopathy” SIC, with a SIC score >4 indicative of early phase DIC[10]. Tang et al. demonstrated lower 28-day mortality with SIC score >4 (40% vs. 64%; p=0.029) and D-dimer >6 fold UNL (33% vs. 52%; p=0.017) in those with vs. without anticoagulation. While SIC score use remains unvalidated in pregnancy, given the poor prognostic implication of high D-dimers and benefit of anticoagulation prophylaxis in non-pregnant individuals with COVID19, consideration of prophylactic LMWH may be valuable in the immediate postpartum period. While Huang et al. did not observe significant APTT elevations with COVID19 outside pregnancy[7], Tang et al. noted increased mortality with high APTT, PT, D-dimer, and fibrin

degradation products compared to COVID19 survivors[8]. Neither APTT nor low fibrinogen was assessed in a pregnancy series[11], although both are part of DIC classification[10].

Two guidelines addressing coagulopathy in COVID19[9, 12] highlight D-dimer elevation, thrombocytopenia and low fibrinogen as poor prognostic indicators of mortality risk. In pregnancy, low fibrinogen was the only coagulation parameter associated with PPH severity; with a positive predictive value of 100% with fibrinogen <2g/L[13]. C1 demonstrated a rapid deterioration of fibrinogen (4.9 to 2.2g/L) and sustained a severe PPH of 1.5 litres. Whilst C2 did not experience excessive bleeding, the sharp drop in fibrinogen to 0.8g/L was treated pre-operatively.

Lymphocytes have a critical role in the immune response to viral infections, with lymphopenia correlating with illness severity and hospitalization in COVID19[14]. In a series from Wuhan, China, including 52 critically ill patients, lymphopenia occurred in 80%[15]. Both C1 and C2 had lymphocyte count nadirs of 0.16 and 0.32, respectively. Both also displayed transaminitis (Table 1). Previous experience with SARS and MERS-CoV revealed transaminitis in 60% of cases[16]. With COVID19, at least seven large scale case series showed the presence of transaminitis in 14-53% of cases during disease progression[16].

We highlight a possible link between third-trimester maternal COVID19 infection and rapid maternal deterioration, with progressive coagulopathy, improving shortly after delivery. To date, no maternal mortality in COVID19 has been reported; however, as pregnancy may not protect COVID19 patients from coagulopathy, and coagulopathy is linked to poorer prognosis outside of pregnancy, it may presage impending compromise. The described laboratory derangements can be reminiscent of HELLP syndrome, and thus knowledge of the COVID19 relationship is paramount for appropriate diagnosis and treatment. As per ISTH recommendations, routine measurements of D-dimers, prothrombin time, and platelet count in all patients presenting with COVID19 may aid risk stratification. In pregnancy, the measurement of APTT and fibrinogen levels may also be valuable.

Authorship Contributions

Dr Vlachodimitropoulou and Dr Malinowski wrote the first draft and this was edited by all authors

Conflicts of Interests

There are no conflicts of interest

Table 1. Investigations and results timeline

Laboratory parameters	Normal Range	Case#	Baseline	2 days Pre-op	1day Pre-op	Delivery Day	POD1	POD2	POD3
Blood									
Hemoglobin (g/L)	110-150	C1	130	123	113	123	110	95	93
		C2	130		127	120	96	88	84
White cell count (x 10^9/L)	3.0-10.0	C1	3.03	0.51	1.06	2.29	3.87	6.32	12.42
		C2	8.65		4.56	2.17	4.86	5.84	4.58
Neutrophil count (x 10^9/L)	1.5-7.0	C1	0.33	0.07	0.33	0.61	1.15	4.44	6.65
		C2			4.01	1.50		4.44	
Lymphocyte count (x 10^9/L)	1.0-3.5	C1	1.52	0.16	0.40	0.77	0.85	2.31	3.42
		C2			0.32	0.54		1.02	
Platelet count (x 10^9/L)	140-400	C1	167	127	98	82	78	86	81
		C2	242	118	63	54	71	89	114
INR	0.9-1.1	C1		1.0		1.0	1.0	1.0	0.9
		C2			1.0	1.1	0.9	0.9	0.9
APTT (seconds)	18.5-29.9	C1		30.3		41.0	41.2	32.3	29.6
	28.0-41.9	C2			51	60	38	38	37
Fibrinogen (g/L)	1.5-4.2	C1		4.9		2.2	2.4	2.6	3.5
	3.7-6.2	C2			3.5	0.8	1.4		4.5
D-Dimer* (mg/L)	0.13-1.7 (3rd Trimester)	C1		2.06		25.79	28.79	2.03	3.99
		C2				>20			1.12
Bilirubin (total) (µmol/L)	3.0-20.0	C1				6	4	3	
		C2			6	10	7	4	4
Creatinine (µmol/L)	45-80	C1	51	68	70	76	67	72	68
		C2				39	51	46	56
AST (unit/L)	13-37	C1	20			52	67	85	83
		C2		33	75	81	112	55	32

ALT (unit/L)	10-40	C1	12			20	20	33	34
		C2		37	47	41	100	76	51
Lactic acid (mmol/L)	0.5-2.0	C1				2.1	3.3		
		C2							
LDH (unit/L)	135-225	C1					494		
		C2					386	304	246
Uric acid umol/L	180-360	C1					187		
		C2							
Creatinine kinase (unit/L)	0.0-190	C1					404		302
		C2							
C-reactive protein (mg/L)	<10.0	C1					44.7		
		C2			92	37	51	139	123
Ferritin (µg/L)	7-191	C1					209		
		C2				431	384		179
Blood culture		C1		-ve					
		C2							
Urine									
Urine Pr:Cr Ratio	0.0-20.0	C1					<19.0		
		C2							
Urine culture		C1		-ve					
		C2			-ve				

*C1 - Dimer Innovance; C2 - D-Dimer STA-Liatest D-Di Plus

ALT indicates alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; INR, international normalized ratio; LDH, Lactate Dehydrogenase; Pr:Cr, protein to creatinine ratio

References

1 RCOG. COVID-19 virus infection and pregnancy. Occupational health advice for employers and pregnant women during the COVID-19 pandemic. Royal College of Obstetrics and Gynaecology, United Kingdom, 2020.

2 Dashraath P, Jing Lin Jeslyn W, Mei Xian Karen L, Li Min L, Sarah L, Biswas A, Arjandas Choolani M, Mattar C, Lin SL. Coronavirus Disease 2019 (COVID-19) Pandemic and Pregnancy. *Am J Obstet Gynecol*. 2020. 10.1016/j.ajog.2020.03.021.

3 Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, Vecchiet J, Nappi L, Scambia G, Berghella V, D'Antonio F. Outcome of Coronavirus spectrum infections (SARS, MERS, COVID 1 -19) during pregnancy: a systematic review and meta-analysis. *American Journal of Obstetrics & Gynecology MFM*. 2020: 100107. https://doi.org/10.1016/j.ajogmf.2020.100107.

4 Sara, N. Iqbal MDROMDNMMDH, Saeed MD, Stacey Gold MDTAMDM-U, Mirza MDM-ERMD. An uncomplicated delivery in a patient with Covid-19 in the United States. 2020.

5 Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. *Obstet Gynecol*. 2009; **114**: 1326-31. 10.1097/AOG.0b013e3181c2bde8.

6 Zeidler C, Grote UA, Nickel A, Brand B, Carlsson G, Cortesão E, Dufour C, Duhem C, Notheis G, Papadaki HA, Tamary H, Tjønnfjord GE, Tucci F, Van Droogenbroeck J, Vermylen C, Voglova J, Xicoy B, Welte K. Outcome and management of pregnancies in severe chronic neutropenia patients by the European Branch of the Severe Chronic Neutropenia International Registry. *Haematologica*. 2014; **99**: 1395-402. 10.3324/haematol.2013.099101.

7 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. *Lancet*. 2020; **395**: 497-506. 10.1016/S0140-6736(20)30183-5.

8 Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020. 10.1111/jth.14768.

9 Jecko Thachil NT, Satoshi Gando, Anna Falanga, Marco Cattaneo, Marcel Levi, Cary Clark, Toshiaki Iba. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. 2020.

10 Iba T, Levy JH, Warkentin TE, Thachil J, van der Poll T, Levi M, the Scientific and Standardization Committee on DIC atSaSCoPaCCotISoTaH. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. *Journal of Thrombosis and Haemostasis*. 2019; **17**: 1989-94. 10.1111/jth.14578.

11 Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, Li J, Zhao D, Xu D, Gong Q, Liao J, Yang H, Hou W, Zhang Y. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *The Lancet*. 2020; **395**: 809-15. 10.1016/S0140-6736(20)30360-3.

12 Beverley Hunt AR, Claire McClintock. Practical guidance for the prevention of thrombosis and management of coagulopathy and disseminated intravascular coagulation of patients infected with COVID-19. 2020.

13 Charbit B, Mandelbrot L, Samain E, Baron G, Haddaoui B, Keita H, Sibony O, Mahieu-Caputo D, Hurtaud-Roux MF, Huisse MG, Denninger MH, de Prost D, Group PS. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. *J Thromb Haemost*. 2007; **5**: 266-73. 10.1111/j.1538-7836.2007.02297.x.

14 Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang Y-Q, Wang Q, Miao H. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduction and Targeted Therapy*. 2020; **5**: 33. 10.1038/s41392-020-0148-4.

15 Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020. 10.1016/S2213-2600(20)30079-5.

16 Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol*. 2020. 10.1016/S2468-1253(20)30057-1.