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Bleeding Diathesis or Prothrombotic State, Which One Predict the COVID-19 Prognosis in Pregnancy?

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ABSTRACT

Since the first reported respiratory distress syndrome due to the new version of the coronaviruses family, COVID-19, there is a concern about the possible maternal and perinatal outcome of new infection in a short and even long time, our information about the prognosis of pregnancy in sync with COVID-19 is limited. What is our task as scientists in eliminating the unknown facts? Here we try to present a couple of pregnant cases in their third trimesters of pregnancy that complicated with two contrary complication of COVID-19 infection, intending to illuminate the best management strategy in COVID-19 infected pregnant. The first case had experienced thromboembolism, and also bleeding accident, who fortunately survived unlike the other case, who expired due to multi-organ failure and impossibility of anticoagulant agent administration for the suspected pulmonary thromboembolic accident. The prior report revealed the thrombo-inflammatory and hypoxic effect of COVID-19 that could lead to microvascular thrombosis and progression, which enforce health care providers, introducing the anticoagulant agents to decline COVID-19 mortality, especially in a critically ill patient. Pregnancy is associated with coagulation abnormality which could intensify the COVID-19-induced coagulopathy. But, one should balance the harm and benefit of such a hazard approach, is there any concern about vascular damage of COVID-19 and subsequent bleeding, that could be exacerbated with high dose anticoagulant agent administration? The other question that we want to discuss in the present report is about comparing the cost and benefit of anticoagulant therapy?

Keywords: Bleeding, COVID-19, Maternal outcome, Morbidity, Perinatal outcome, Pregnancy, Thromboembolism

Introduction

Since the world organization announcement for an emergent situation due to the novel Coronavirus pandemic, this virus has shown aggressive nature, different manifestations, and a high fatality rate. Venous thromboembolism (VTE) be considered as one of the profound features in this regard, as there is a strong suggestion on the need for thrombo-prophylaxis in confirmed cases **(1-3)**. As there is no relevant evidence on the susceptibility of pregnant cases with under-ling physiologic changes for this viral infection in comparison with prior coronaviruses epidemics, **(4-6)** and above that the least hazard management in this population, in the present study we aim to discuss this challenging issue, by introducing a pair of pregnant cases with the discrete outcome and reviewing others advice **(7)**.

Material and Method

A couple of pregnant-cases have been selected from the hospitalized patient in a level 3 maternity hospital in Iran, with a certain diagnosis of COVID-19 based on reverse transcription-polymerase chain reaction (RT-PCR) on a nasopharyngeal and oropharyngeal specimen and presence of ground-glass-opacities in the chest-CT scan. The ethical committees' rules are considered in this report. The patient signed the informed consent in the aim of reporting the present article.

Finding

There were 2 admitted pregnant-cases (gravida 2, para1) with a similar presentation, fever, myalgia, respiratory discomfort, and tachycardia (between 120-140beat/min) but normal peripheral oxygen saturation (O2Sat). Although the administration of broad-spectrum antibiotics, prophylactic anti-coagulant, hydroxyl-chloroquine, and Atazanavir was considered,

the prog-nosis was not favorable; both cases experienced mate-rnal morbidity or mortality.

Case 1

A 32-year-old gravida woman at 34/3 weeks of gestation (GW) with a history of diet-controlled gestational diabetes, hypothyroidism, and recent contact with multiple cases of confirmed COVID-19 was admitted with a typical presentation. Deteriorating symptoms in subsequent days (Table 1), lead to a diagnosis of pulmonary thromboembolic accident (PTE) based on an MDCT scan (Figure 1), so anticoagulant-agent was prescribed in therapeutic dose. Despite, a dramatic response in respiratory status, a sudden sever vaginal-bleeding accident, because of placental abruption, ended up to emergent caesarian delivery. Now, after 6 weeks of termination, both patient and her-male fetus are in complete remission.

Case 2

A 21-year-old gravida woman at 21 GW had been referred with a similar presentation. But due to deteriorating symptoms within 48 hours with no response to vasopressors agent, intubation was planned for her (Table 2, Figure 2). Despite all efforts, unjustified uterine contractions ended up in spontaneous delivery of a nonviable male neonate, what lately considered because of placental thrombosis. Although patient-health status, had initially shown an affirmative response to daily-plasmapheresis, on HD28, her condition regressed again and PTE was suggested based on elevated Pulmonary arterial pressure (in about 45-50) and heart failure (EF near15%). Unfortunately, there was no permission for anticoagulant therapy initiation because of thrombocytopenia and coagulopathy and she died over the next two days by worsening of cardiopulmonary status.

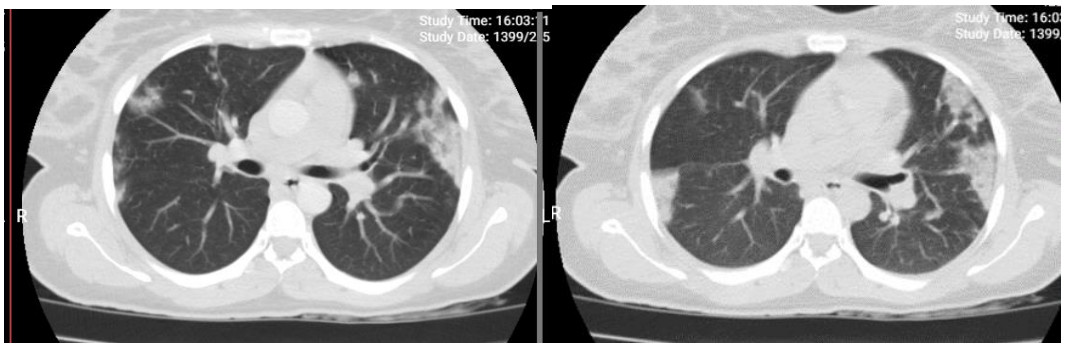

Figure 1. Chest HRCT of the patient during hospitalization: bilateral peripheral grand glass opacity

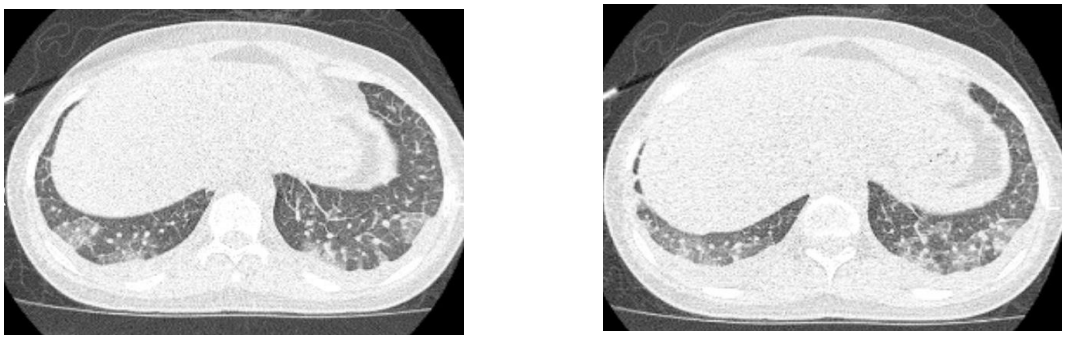

Figure 2. Chest HRCT of the patient during hospitalization: bilateral peripheral grand glass opacity

Table 1. Laboratory Data of second patient during hospitalization

	Firth day of admission	Second day of admission	Third day of admission	Eight day of admission	Last day of admission
Leukocytes × 10 /L	7000	7200	13100	5100	15400
Lymphocytes, %	20	13.7	8.4	27	18
Neutrophils, %	75	84.3	90	63	78
Platelets × 109/micL	155000	173000	200000	239000	251000
Hemoglobin, gr/dL	12.7	13	12.9	11.8	10.1
ESR, mm/h	29	NA	NA	NA	NA

	Firth day of admission	Second day of admission	Third day of admission	Eight day of admission	Last day of admission
CRP, mg/L	39	45	NA	NA	NA
Creatinine, mg/dL	0.9	0.9	0.9	0.8	0.7
BUN mg/dL	7	10	10	8	6
Na, mEq/L	137	138	137	142	141
Ka, mEq/L	4.5	4.7	4.5	3.5	3.9
Protein (U/A)	neg	NA	NA	NA	NA
Blood (U/A)	neg	NA	NA	NA	NA
WBCs, hpf (U/A)	neg	NA	NA	NA	NA
RBCs, hpf (U/A)	neg	NA	NA	NA	NA
Pr/Cr(U/A)	0.1	NA	NA	NA	NA
Albumin, g/L	3.5	3.5	NA	NA	NA
AST, U/L	24	25	NA	NA	NA
ALT, U/L	10	8	NA	NA	NA
Bilirubin	0.4	0.6	NA	NA	NA
LDH, U/L	518	590	NA	NA	NA
D-Dimer(µg/mL)	3.1	2.6	1.9	1.6	1.3
FDP	24	24	NA	NA	NA
CPK U/L	71	NA	NA	NA	NA
PT, seconds	11.4	11	11	NA	27.5
PTT, seconds	47	50	56	50	55
INR	1	1	1	NA	2.5
Fibrinogen	300	302	NA	NA	NA
Cardiac troponins	0.2	NA	NA	NA	NA
Ferritin	81	NA	NA	NA	NA
Procalcitonin (µg/L)	0.4	NA	NA	NA	NA
TSH	0.75	NA	NA	NA	NA

Table 2. Laboratory Data of second patient during hospitalization

	First day of hospitalization	First day of ICU admission	Second day of ICU admission	The day after 7 session of plasma exchange	Third weeks of hospitalization	Fourth weeks of hospitalization	Last day of hospitalization
Leukocytes × 10 /L	4300	3900	10500	13200	15100	8200	5000
Lymphocytes, %	25	20	17	22	3.4	4.7	11
Neutrophils, %	71	77	80	73	94	92	84
Platelets × 109/micL	71000	59000	33000	56000	70000	41000	36000
Hemoglobin, gr/dL	10.6	10.7	8.4	7.9	11	7.8	7.3
ESR, mm/h	23	NA	NA	NA	NA	NA	NA
CRP, mg/L	55	58	51	27	71	110	
Creatinine, mg/dL	0.8	1	2.5	3.4	4.4	3	2.4
BUN mg/dL	7	9	23	63	78	73	60
Na, mEq/L	131	145	150	148	135	131	136
Ka, mEq/L	3	4.7	4.6	4	4.6	4.3	4.2
Protein (U/A)	1+	NA	NA	NA	NA	NA	NA

	First day of hospitalization	First day of ICU admission	Second day of ICU admission	The day after 7 session of plasma exchange	Third weeks of hospitalization	Fourth weeks of hospitalization	Last day of hospitalization
Blood (U/A)	trace	NA	NA	NA	NA	NA	NA
WBCs, hpf (U/A)	1-2	NA	NA	NA	NA	NA	NA
RBCs, hpf (U/A)	Neg	NA	NA	NA	NA	NA	NA
Pr/Cr(U/A)	0.9	NA	NA	NA	NA	NA	NA
Albumin, g/L	3.4	NA	NA	NA	NA	NA	NA
AST (U/L)	107	500	3126	110	30	26	30
ALT (U/L)	96	216	1500	44	13	20	25
Bilirubin	2.9	NA	6.9	3.8	3.3	3.4	2.4
LDH (U/L)	746	4051	4061	1457	1096	823	705
D-Dimer (µg/ml)	>10	NA	>10	6.3	>5	2.5	3.3
FDP	45	NA	NA	NA	45	39	NA
CPK U/L	123	NA	NA	NA	NA	NA	NA
PT, seconds	16	19.5	21	11.9	12.3	NA	13
PTT, seconds	48	68	65	36	39	34	35
INR	1.48	1.77	2	1.08	1.17	NA	1.1
Fibrinogen	237	242	201	285	211	242	246
Cardiac troponins	<0.02	NA	NA	NA	NA	NA	NA
Ferritin	NA	739	>1650	NA	NA	NA	NA
procalcitonin(µg/l)	NA	>10	NA	0.5	7.5	NA	NA
APS test	NA	normal	NA	NA	NA	NA	NA

Discussion

The restricted data on the COVID-19 in pregnancy and its exact management warranted more attempt to study this virus's mechanism of action. Above, the suggested association of COVID-19 with inflammatory cytokine crisis, endothelial damage, and overexpression of tissue factor, it sounds the COVID-19-induced hypoxia could cause marked blood viscosity and hyper coagulative state **(7-9)**. Although the effectiveness of elevated D-dimer in the prediction of thrombo-inflammatory complication of COVID-19 is suggested in the present report, its pregnancy accuracy is on the debate **(8)**. Taking into account the progressive course of illness in present cases with elevated D-dimer, there is an obvious need for more study on the potential usage of D-dimer in the hospitalization of COVID-19 patients. The other concern about COVID-19 and pregnancy is the duplicated chance of VTE, so, is it reasonable to prescribe higher-dose of the anticoagulant agent in this population? There is a contrary feature by this virus, thrombin generative tendency as described before, and on the other hand bleeding potential due to dysfunction of the angiotensin-converting enzyme (ACE) 2 receptor and endothelial cell damage, **(10, 11)** Considering the potential side-effect of anticoagulant and besides, the parallel complication in COVID-19 makes this suggestion more complex. Moreover, one should justify the risk of perinatal morbidity in comparison with maternal outcome **(5, 9)**. Hypoxic effect of COVID-19 on the placenta and risk of thrombosis and abruption, and also inflammatory-induced endothelial cell damage and bleeding threat should be mentioned at the time of anticoagulants administration **(12-14)**.

Conclusion

Although there is minimal supporting data, the need for prescribing the risk-based-adjusted dose of an anticoagulant agent in the aim of eliminating the bleeding potential sounds essential. But, according to the documented benefit of anticoagulant prescription in COVID-19 cases with positive predictive factor, and the bleeding tendency of either COVID-19-induced circumstance or the anticoagulant agent, is there an underestimated need for hospitalization and monitoring of high-risk pregnant population during their treatment?

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Conflict of Interest

The authors declared no conflicts of interest.

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