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Preeclampsia-like syndrome induced by severe COVID-19: a prospective observational study

Short title: Preeclampsia-like syndrome in COVID-19

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ABSTRACT

Objectives

To investigate the incidence of clinical, ultrasonographic and biochemical findings related to preeclampsia (PE) in pregnancies with COVID-19, and to assess their accuracy to differentiate between PE and the PE-like features associated with COVID-19.

Design: A prospective, observational study.

Setting: Tertiary referral hospital.

Participants: Singleton pregnancies with COVID-19 at >20+0 weeks.

Methods: 42 consecutive pregnancies were recruited and classified into two groups: severe and nonsevere COVID-19, according to the occurrence of severe pneumonia. Uterine artery pulsatility index (UtAPI) and angiogenic factors (soluble fms-like tyrosine kinase-1/placental growth factor [sFlt-1/PlGF]) were assessed in women with suspected PE.

Main outcome measures: Incidence of signs and symptoms related to PE, such as hypertension, proteinuria, thrombocytopenia, elevated liver enzymes, abnormal UtAPI and increased sFlt-1/PlGF.

Results

34 cases were classified as nonsevere and 8 as severe COVID-19. Six (14.3%) women presented signs and symptoms of PE, all six being among the severe COVID-19 cases (75.0%). However, abnormal sFlt-1/PlGF and UtAPI could only be demonstrated in one case. Two cases remained pregnant after recovery from severe pneumonia and had a spontaneous resolution of the PE-like syndrome.

Conclusions

Pregnant women with severe COVID-19 can develop a PE-like syndrome that might be distinguished from actual PE by sFlt-1/PlGF, LDH and UtAPI assessment. Health care providers should be aware of its existence and monitor pregnancies with suspected preeclampsia with caution.

Funding: None.

Keywords: angiogenic factors; COVID-19; PlGF; preeclampsia; preeclampsia-like syndrome; pregnancy; SARS; SARS-CoV-2; sFlt-1

Tweetable abstract: This study shows that a preeclampsia-like syndrome could be present in some pregnancies with severe COVID-19.

INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) declared the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak a pandemic disease, given its increasing number of cases worldwide.[1] Studies have shown that the disease caused by SARS-CoV-2, named as COVID-19 (coronavirus disease 2019) typically presents with fever, dry cough, and fatigue; nevertheless, up to 14% of the cases can evolve to severe pneumonia and 5% to severe acute respiratory syndrome (SARS) both requiring admission to intensive care for intensive respiratory support.[2] Whereas COVID-19 is primarily a respiratory infection, it has important systemic effects including hypertension, kidney disease, thrombocytopenia, and liver injury.[3–6] Since SARS-CoV-2 is believed to invade the host through the cell entry receptor angiotensin-converting enzyme 2 (ACE2), these signs and symptoms in SARS-CoV-2 infection are thought to be due to the vasoconstriction resulting from the dysfunction of the renin-angiotensin system.[7,8] By contrast, clinical features of preeclampsia (PE) are mainly consequence of the endothelial damage originated by placental oxidative stress and antiangiogenic status, which leads to the appearance of hypertension and proteinuria, elevated liver enzymes, renal failure, or thrombocytopenia among others.[9,10] An increased incidence of PE has been reported among mothers infected with SARS-CoV-2 compared to general population.[11] Misdiagnosis, however, might have occurred in some of these cases since COVID-19 and PE have overlapping clinical features. Therefore, differential diagnosis might be challenging in COVID-19 pregnant women presenting with hypertension and proteinuria, thrombocytopenia, or elevated liver enzymes.[10] Thus, the aim of this study was to investigate the prevalence of clinical, ultrasonographic, and biochemical findings related to PE in women with SARS-CoV-2 infection and to assess their accuracy to differentiate between actual PE and PE-like features associated with COVID-19.

METHODS

We carried out a prospective cohort study of all consecutive pregnant women at >20 weeks of gestation that presented to the emergency department of our tertiary care center for suspicion of COVID-19 (dry cough and fever) and had laboratory-confirmed SARS-CoV-2 infection, between March 13, and April 10, 2020. Patients were not actively involved in the research.

Patients were classified in two groups: severe and non-severe COVID-19, according to the occurrence of severe pneumonia. The laboratory and clinical data were prospectively recorded in a

database. The recorded data included the following: platelet count (per microliter), D-dimer (μg/L), lactate dehydrogenase (U/L), aspartate aminotransferase (U/L), alanine amninotransferase (U/L), urine protein to creatinine ratio (mg/g), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), mean arterial pressure (mmHg), creatinine (mg/dL), and gestational age (GA) in weeks. GA to describe particular cases was expressed in weeks + days. Mean arterial pressure was calculated as: 1/3*(systolic blood pressure) + 2/3*(diastolic blood pressure). Maternal baseline characteristics were compared between groups. In severe cases, data was analyzed at three different moments during COVID-19: before, during, and after intensive care unit (ICU) admission for severe pneumonia.

According to the WHO guidance, laboratory confirmation for SARS-CoV-2 was defined as a positive result of real-time reverse transcriptase–polymerase chain reaction (RTPCR) assay of nasal and pharyngeal swabs.[12]

PE was defined as new onset of high blood pressure (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) or worsening of previous high blood pressure added to new onset proteinuria (protein to creatinine ratio >300) or worsening of previous proteinuria, or to at least one of the following signs and symptoms of severe PE: cerebral or visual symptoms, elevation of liver enzymes to twice normal concentration, platelet count less than 100,000/μL, serum creatinine concentrations greater than 1.1 mg/dL, or pulmonary edema.[10] The HELLP syndrome is frequently considered a variant of PE. Diagnostic criteria for HELLP syndrome are haemolysis with increased LDH (> 600 U/L) and AST (≥ 70 U/L), and platelets < 100,000/μL.[13]

In women with new-onset hypertension, uterine artery pulsatility index (UtAPI) was assessed by transabdominal Doppler ultrasound and maternal serum levels of placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) in pg/mL were determined by means of the fully automated Elecsys assays for sFlt-1 and PlGF on an electrochemiluminescenceimmunoassay platform (cobas e analyzers; Roche® Diagnostics, Rotkreuz, Switzerland).[14,15] The sFlt-1/PlGF was then calculated. UtAPI above the 95th centile for gestational age, and sFlt-1/PlGF values ≥85 (at <34 weeks) or ≥110 (at ≥34 weeks) were considered highly suggestive of underlying placental disease.[16–19]

Statistical analysis

R Commander, R package version 2.3-1 software was used for statistical analysis. Categorical data were reported as frequency and percentage and comparisons between severity groups were estimated by chi-square or Fisher tests, as appropriate. Continuous variables were described as median and interquartile (IQR) range and Mann-Whitney U test was used to assess differences between severity groups. Statistical significance level was set at $p<0.05$.

RESULTS

During the study period (31 days), 42 cases of SARS-CoV-2 infected women were identified at a median GA of 32.0 (IQR 26.0-37.5) weeks of gestation. Among them, eight (19.0%) cases developed severe pneumonia and required admission to the ICU. Median maternal age of cases with severe COVID-19 was significantly greater than in the nonsevere cases (39.4 [34.2-44.5] vs. 30.9 [25.0-41.8], p=0.006). No other pregnancy baseline characteristics differed between severity groups. Among the eight severe cases, six (75.0%) developed PE features (new onset hypertension and proteinuria and/or thrombocytopenia and/or, elevated liver enzymes), requiring antihypertensive drugs in all of them. No cases with diagnostic criteria for PE were found among the 34 nonsevere COVID-19 women (Table 1).

Evolution of clinical and laboratory findings in the severe cases of COVID-19

Before severe pneumonia, all eight women were normotensive, had normal platelet count, liver enzymes, LDH, and proteinuria and only one case with UtAPI above the 95th centile was identified. During severe pneumonia, the most frequent findings were: elevated liver enzymes to twice normal concentrations (87.5%), proteinuria >300mg/g (75.0%), and hypertension (62.5%) (Figure 1). No cases with creatinine >1.1mg/dL or platelet count <100,000/μL were found; nevertheless, one case presented mild thrombocytopenia (platelet count <150,000/μL). sFlt-1/PlGF ≥85/110 and UtAPI >95th centile were present only in one woman. Only one case with LDH >600 UI/L was identified. As a result of these findings, six (75.0%) had diagnostic criteria of PE and/or HELLP syndrome. Cesarean delivery was performed during ICU stay in four cases. HELLP syndrome was the indication for delivery in case 1 (at a GA of 30+1) and SARS worsening in cases 3, 4, and 7 (at a GA of 37+6, 36+6, and 28+3, respectively). After recovery from severe pneumonia, hypertensive therapy was no longer required in all cases and only the woman that had presented the sFlt-1/PlGF >110, LDH>600 and UtAPI above the 95th centile,

remained with PE diagnostic criteria (more details on clinical and laboratory findings and their evolution in severe cases can be seen in Table 2 and Figure 1).

DISCUSSION

Main findings

This study shows that 14.3% of COVID-19 pregnant women develop PE features; however, they only appeared in COVID-19 cases complicated by severe pneumonia. In this situation, PE/HELLP diagnostic criteria were found in 6 (75.0%) of the cases; nevertheless, abnormal angiogenic status, increased LDH and placental underperfusion could only be confirmed in one of them, which indicates that this case was probably an actual PE. These findings suggest that the signs and symptoms compatible with PE/HELLP present in five out of these six cases, could be derived from the complex polypharmacy administrated or from the renal and cardiovascular dysfunction for severe SARS-CoV-2 infection. In our cohort, only two of these six cases remained pregnant after severe pneumonia recovery, and then, all PE/HELLP features recovered spontaneously. PE and HELLP syndrome do not resolve spontaneously and delivery is the only definitive cure. For these reasons, we believe that the five women with PE/HELLP signs and symptoms, and normal sFlt-1/PlGF, UtAPI and LDH<600, had developed a PE-like syndrome.

Strengths and limitations

To our knowledge this is the first study to describe the incidence of signs and symptoms of PE in a relatively large cohort of pregnancies with COVID-19 and to show that a PE-like syndrome could be induced by severe COVID-19. Furthermore, our findings are of great value to improve maternal care of pregnancies with severe pneumonia due to COVID-19.

This study has several limitations. First, this is a small series and the results should be considered with caution. Further research is needed to better understand the systemic consequences of COVID-19 in pregnant women.. Second, only five women with PE-like syndrome are reported, which could make our findings not applicable to all pregnancies with severe pneumonia due to COVID-19. Third, only two of the five women that developed a PE-like syndrome remained pregnant after severe pneumonia and despite the PE-like syndrome recovered spontaneously in both, we cannot affirm that the three other cases did not improve due to delivery. Nevertheless, we believe that the PE-like syndrome alone may not be an obstetric indication for delivery, since it

seems that it might not be a placental complication itself, but one of the clinical manifestations of severe COVID-19. Finally, although UtAPI and sFlt-1/PlGF ratio have a high negative predictive value to predict the short-term absence of PE, they are not diagnostic criteria of PE;[27,28] thus, we cannot categorically state that the case with PE features and elevated UtAPI and sFlt-1/PlGF was an actual PE and not a PE-like syndrome.

Interpretation

Several disorders have previously proved to imitate PE since they share some of the clinical and laboratory findings of patients with PE. The pathophysiologic causes of these conditions include vasospasm, platelet activation or destruction, microvascular thrombosis, endothelial cell dysfunction, and reduced tissue perfusion. Some of these disorders include gestational hypertension, chronic kidney disease, acute fatty liver of pregnancy, thrombotic thrombocytopenic purpura, haemolytic uremic syndrome, acute exacerbation of systemic lupus erythematosus, severe hypothyroidism, and sepsis.[17,20,21] Differential diagnosis may be a challenge to caregivers due to the overlap of diagnostic criteria among them. Additionally, some of them are potentially life-threatening for both the mother and the fetus; thus, accurate diagnosis is important since the management and prognosis of these conditions differ widely. Recent studies have shown that angiogenic factors support the differential diagnosis between PE and some of its imitators.[17,22,23] PlGF and sFlt-1 are placenta-related angiogenic factors that are highly specific of placental insufficiency.[24] In PE, the placenta fails to properly invade and remodel maternal uterine spiral arteries, leading to impaired perfusion and placental oxidative stress.[25,26] This condition leads to increased UtAPI and to an antiangiogenic status with increased s-Flt-1/PlGF ratio due to up-regulation of sFlt-1 and down-regulation of PlGF.[9,27] The identification of an sFlt-1/PlGF imbalance is detectable in the maternal circulation at least five weeks before the onset of clinical PE.[24] Thus, COVID-19 patients with normal early phase of placental implantation should have normal values of sFlt-1/PlGF and UtAPI in spite of proteinuria, thrombocytopenia, elevated liver enzymes, or hypertension. This hypothesis, however, had not been previously investigated due to the very recent outbreak of the SARS-CoV-2 infection.

This study has important clinical implications as we show that sFlt-1/PlGF, UtAPI and LDH permit differentiating PE from the PE-like syndrome present in some of the pregnant women with severe COVID-19. This knowledge could improve management and reduce misdiagnosis in

pregnancies with severe COVID-19. In our cohort, the case 1 was probably misdiagnosed as HELLP syndrome which in addition to the concurrence of SARS, influenced the indication of delivery. The fact that the sFlt-1/PlGF results were not available at the time of maternal condition worsening, and the scarce evidence available at that time of the consequences of COVID-19 during pregnancy, prompted the delivery indication at 30+1 weeks. After the experience with this first case, a more conservative management was adopted in the following cases that developed PE-like syndrome. Fortunately, they completely recovered after severe pneumonia and became normotensive again with no antihypertensive drugs and without being delivered.

Conclusion

Pregnant women with severe COVID-19 could develop a PE-like syndrome, which might be distinguished from actual PE by sFlt-1/PlGF, LDH and UtAPI assessment. Therefore, health care providers should be aware of its existence and monitor pregnancies with suspected PE with caution. PE-like syndrome might not be an indication for earlier delivery in itself since it might not be a placental complication and could resolve spontaneously after recovery from severe pneumonia.

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Disclosure of interests

Manel Mendoza and Itziar Garcia received lecture fees by Roche diagnostics. The other authors have no conflicts of interest to declare. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

AS and EC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. EC, AS, MM, and IGR conceived and designed the study. RMLM, JB, NM, and NFH contributed to the literature research. NM, CR, PGM, and BS contributed to data collection and confirmation. MM, IGR, and AS contributed to data analysis, and MM, IGR, AS, RMLM, JB, NFH and EC contributed to data interpretation. MM and IGR were in charge of writing the manuscript draft. AS and EC made substantial revisions to the manuscript. MM and IGR contributed equally to this article. AS and EC contributed equally to this article.

Details of ethics approval

This study was approved by the Vall d'Hebron University Hospital Ethics Committee (PR(AMI)181/2020) on March 13, 2020. Written informed consent was waived due to the rapid emergence of this infectous disease. However, verbal informed consent was obtained in all patients, which was included in the patient's medical record.

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28. 1 Recommendations | PlGF-based testing to help diagnose suspected pre-eclampsia (Triage PlGF test, Elecsys immunoassay sFlt-1/PlGF ratio, DELFIA Xpress PlGF 1-2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio). NICE Guidance. https://www.nice.org.uk/guidance/dg23/chapter/1-Recommendations. (accessed Mar 28, 2020.

Table 1. Maternal characteristics in pregnant women with COVID-19.

	All patients (n=42)	Nonsevere patients (n=34)	Severe patients (n=8)	p
Maternal age (years)	32.0 (26.0-37.5)	30.9 (25.0-41.8)	39.4 (34.2-44.5)	0.006
Pre-pregnancy BMI (Kg/m2)	26.2 (23.5-29.3)	26.1 (22.8-29.3)	27.9 (25.4-30.6)	0.378
Gestational age (weeks)	31.6 (25.9-36.1)	32.8 (26.7-36.1)	28.6 (22.3-32.4)	0.211
Ethnicity				0.304
White	22 (52.4%)	19 (55.9%)	3 (37.5%)	
Latin American	17 (40.5%)	12 (35.3%)	5 (62.5%)	
Others	3 (7.1%)	3 (8.8%)	0	
ART	4 (9.5%)	2 (5.9%)	2 (25.0%)	0.158
Smoking	2 (4.8%)	1 (2.9%)	1 (12.5%)	0.348
Nuliparous	20 (47.6%)	16 (47.1%)	4 (50.0%)	1.0
History of PE	0	0	0	1.0
Pre-pregnancy HTN	0	0	0	1.0
Pre-pregnancy Diabetes	1 (2.4%)	1 (2.4%)	0	1.0
Chronic kidney disease	0	0	0	1.0
PE diagnostic criteria during COVID-19	6 (14.3%)	0	6 (75.0%)	<0.001

Continuous data are given as median and interquartile range. Categorical data as frequency and percentage. ART, assisted reproductive technology; BMI, body mass index; HTN, hypertension; PE, preeclampsia. p values denoted the comparison between nonsevere and severe subgroups.

Table 2. Clinical and biochemical preeclampsia-related findings in pregnant women with COVID-19 before, during and after severe pneumonia.

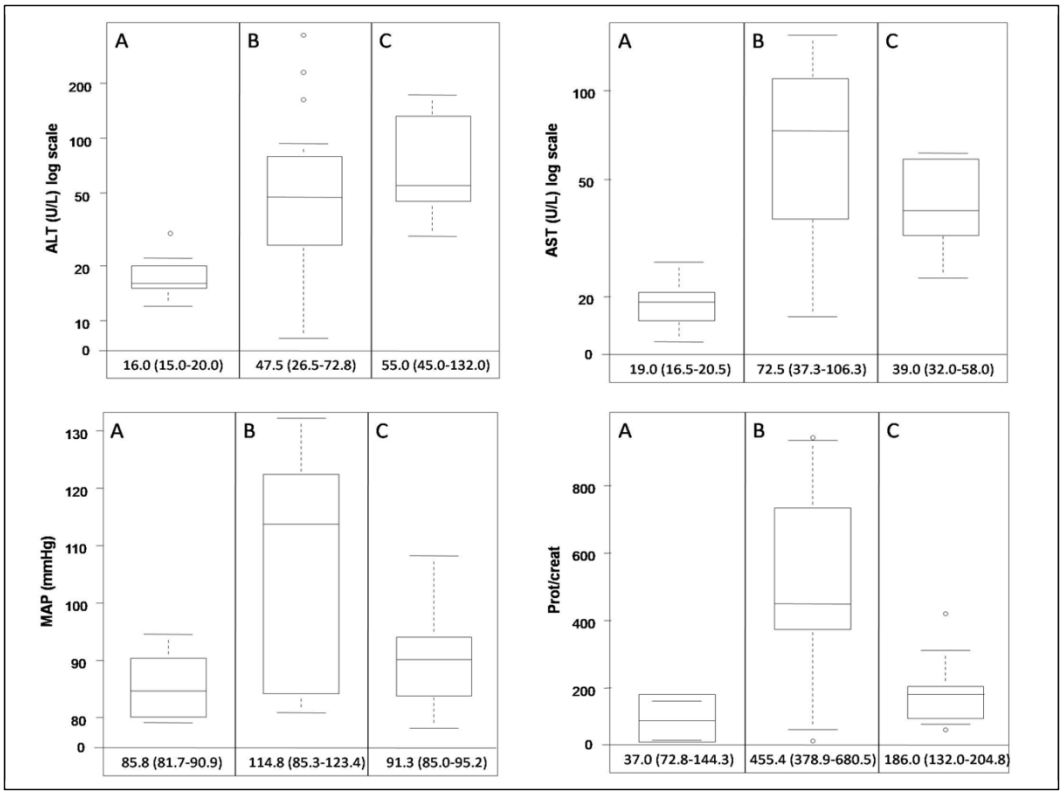
	Variables	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Before severe pneumonia	GA (weeks)	30+0	22+6	37+5	36+4	32+0	20+3	27+4	20+1
	SBP (mmHg)	130	120	123	117	104	135	107	116
	DBP (mmHg)	74	72	74	67	71	76	67	63
	MAP (mmHg)	92.7	88.0	90.3	83.7	82.0	95.7	80.3	80.7
	Prot/creat (mg/g)	37	180	-	-	-	-	-	-
	AST (U/L)	17	19	15	20	26	19	23	14
	ALT (U/L)	16	30	13	26	20	12	14	22
	Platelets/µL	158,000	242,000	402,000	210,000	275,000	234,000	319,000	242,000
	LDH (U/L)	-	-	-	-	-	-	-	-
	D-dimer (mg/mL)	-	-	-	-	-	-	-	-
	Creatinine (mg/dL)	0.63	0.49	-	0.79	0.74	0.36	0.45	0.66
	UtAPI >95th centile	No	No	Yes	No	No	No	No	No
	PE/HELLP diagnostic criteria	No	No	No	No	No	No	No	No
During severe pneumonia	GA (weeks)	30+1	24+4	37+6	36+5	32+1	20+4	28+3	20+2
	SBP (mmHg)	145	168	156	155	116	115	140	108
	DBP (mmHg)	90	116	98	108	70	68	105	69
	MAP (mmHg)	108.3	133.3	117.3	123.7	85.3	83.7	116.7	82.0
	Prot/creat (mg/g)	855	622	378	514	396	49	948	130
	AST (U/L)	153	122	104	62	38	52	138	113
	ALT (U/L)	170	136	52	39	38	14	65	230
	Platelets/µL	324,000	160,000	279,000	231,000	336,000	243,000	108,000	505,000
	LDH (U/L)	482	370	672	555	517	176	463	312
	D-dimer (mg/mL)	457	2,129	5,065	1,800	326	119	514	376
	Creatinine (mg/dL)	0.34	0.42	0.85	0.88	0.42	0.20	0.39	0.26
	Hidralazine	Yes	Yes	Yes	Yes	No	No	No	No
	Labetalol	Yes	Yes	Yes	Yes	No	No	Yes	No
	sFlt-1/PlGF	9.40	20.24	378.90	49.36	24.78	4.60	7.60	5.19
	UtAPI >95th centile	No	No	Yes	No	No	No	No	No
	PE/HELLP diagnostic criteria	Yes	Yes	Yes	Yes	No	No	Yes	Yes
After severe	GA at delivery (weeks)	30+1	Not delivered	37+6	36+6	Not delivered	Not delivered	28+3	Not delivered
	Reason for delivery	HELLP	-	SARS	SARS	-	-	SARS	-

pne	**GA (weeks)**	-	25.5	-	-	33.2	21.5	-	21.3
	SBP (mmHg)	123	132	142	115	116	108	109	110
	DBP (mmHg)	83	75	93	68	79	62	75	64
	MAP (mmHg)	96.3	94.0	109.3	83.7	91.3	77.3	86.3	79.3
	Prot/creat (mg/g)	210	183	426	83	115	83	189	128
	AST (U/L)	39	32	56	43	58	-	23	61
	ALT (U/L)	45	132	41	29	55	-	29	172
	Platelets/µL	312,000	218,000	232,000	258,000	292,000	169,000	364,000	762,000
	LDH (U/L)	222	277	692	325	211	-	353	192
	D-dimer (mg/mL)	617	1,745	3,258	-	454	-	347	470
	Creatinine (mg/dL)	0.25	0.3	0.58	-	0.41	-	0.42	0.65
	UtAPI >95th centile	-	No	-	-	No	No	-	No
	PE/HELLP diagnostic criteria	No	No	Yes	No	No	No	No	No

ALT, alanine amninotransferase; AST, aspartate aminotransferase; DBP, diastolic blood pressure; GA, gestational age; LDH, lactate dehydrogenase; MAP, mean arterial pressure; PE, preeclampsia; PlGF, placental growth factor; prot/creat; urine protein to creatinine ratio; SARS, severe acute respiratory syndrome; sFlt-1, soluble fms-like tyrosine kinase-1; UtAPI, uterine artery pulsatility index.

Figure 1. Evolution of ALT, AST, proteinuria and mean arterial blood pressure in pregnant women with COVID-19 before (A), during (B) and after (C) severe pneumonia.

The bottom and top edges of each box represent the first and third quartiles, respectively, the band within the box represents the median value and the whiskers represent values that are 1.5 times the interquartile range. Median values and interquartile range of each variable are displayed.



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