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Clinical course of Coronavirus Disease-2019 (COVID-19) in pregnancy

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Conflict of Interest

None

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ABSTRACT

Introduction: The aim of this study is to report our clinical experience in the management of pregnant women infected with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) during the first thirty days of the Coronavirus disease (COVID-19) pandemic. **Material and Methods**: We reviewed clinical data from the first 60 pregnant women with COVID-19 whose care was managed at Puerta de Hierro University Hospital, Madrid, Spain from March 14th to April 14th, 2020. Demographic data, clinical findings, laboratory test results, imaging findings, treatment received, and outcomes were collected. An analysis of variance (Kruskal-Wallis test) was performed to compare the medians of laboratory parameters. Fisher's exact test was used to evaluate categorical variables. A correspondence analysis was used to explore associations between variables. **Results**: A total of 60 pregnant women were diagnosed with COVID-19. The most common symptoms were fever and cough (75.5%, each) followed by dyspnea (37.8%). Forty-one patients (68.6%) required hospital admission (18 due to disease worsening and 23 for delivery) of whom 21 patients (35%) underwent pharmacological treatment, including hydroxychloroquine, antivirals, antibiotics and tocilizumab. No renal or cardiac failures or maternal deaths were reported. Lymphopenia (50%), thrombocytopenia (25%), and elevated C-reactive protein (CRP) (59%) were observed in the early stages of the disease. Median CRP, D-dimer and the neutrophil/lymphocyte ratio were elevated. High CRP and D-dimer levels were the parameters most frequently associated with severe pneumonia. The Neutrophil/lymphocyte ratio was found to be the most sensitive marker for disease improvement (relative risk: 6.65; 95% CI: 4.1-5.9). During the study period, 18 of the women (78%) delivered vaginally. All newborns tested negative for SARS-CoV-2 and none of them were infected during breastfeeding. No SARS-CoV-2 was detected in placental tissue. **Conclusions**: Most of the pregnant COVID-19 positive patients had a favorable clinical course. However, one-third of them developed pneumonia, of whom 5% presented a critical clinical status. CRP and D-dimer levels positively correlated with severe pneumonia and the neutrophil/lymphocyte ratio decreased as the patients improved clinically. Seventy-eight percent of patients had a vaginal delivery. No vertical or horizontal transmissions were diagnosed in the neonates during labor or breastfeeding.

Keywords:

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SARS-CoV-2; Coronavirus 2; COVID-19; Severe Acute Respiratory Syndrome; pregnancy; labor; newborn; vertical transmission; breastfeeding.

Abbreviations

COVID-19 Coronavirus disease 2019

SARS-CoV-2 Severe Acute Respiratory Syndrome coronavirus 2

CRP C-reactive protein

RT-PCR reverse transcription polymerase chain reaction

LDH lactate dehydrogenase;

ICU Intensive Care Unit;

NLR neutrophils/lymphocytes ratio;

HELLP hemolysis, elevated liver enzymes, low platelets;

Key Message

Thirty percent of pregnant women with COVID-19 presented with pneumonia. Increased C-reactive protein and D-dimer levels, increased neutrophil/lymphocyte ratios, and lymphopenia were associated with worse outcomes. Vaginal delivery appears to be safe as no neonates were infected at birth.

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INTRODUCTION

The Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) is an RNA virus responsible for the 2019 coronavirus disease (COVID-19).[1] COVID-19 can present with common cold-like symptoms to a more severe disease, such as pneumonia and Severe Acute Respiratory Syndrome, and may cause multiple organ failure and death.

In the three months since the World Health Organization's worldwide Public Health emergency declaration (first COVID-19 case was reported on Dec 31, 2019),[2,3] more than 3,207,543 confirmed cases and 227,379 deaths were reported globally, including 212,917 cases and 24,275 deaths in Spain (as of April 30, 2020).[4] Progression of the COVID-19 disease has been exponential; the first Spanish case was confirmed on Feb 1, 2020 (Canary Islands), followed by a second case ten days later (on the peninsula). Since then, an exponential growth of cases has continued.

The global management of more than 3 million COVID-19 patients within a relatively short period has provided important data on epidemiological characteristics, viral transmission mechanisms, clinical symptoms, diagnosis as well as prevention and treatment of the disease.[1,2-11] However, the knowledge regarding clinical course and management of pregnant women with COVID-19 is still limited. The published literature to date indicates that pregnant women may be more vulnerable to COVID-19. The disease may be associated an increased risk of premature rupture of membranes, preterm delivery, fetal tachycardia, and fetal distress. Lymphocytopenia and elevated C-reactive protein (CRP) levels were observed in the majority of the COVID-19 pregnant women.[12,13] A recently published systematic review suggested that there is a higher risk of severe maternal morbidity and perinatal death associated with COVID-19 infection, although maternal-fetal transmission was not detected.[14]

The aim of our study was to describe our experience in the clinical management of 60 COVID-19 positive pregnant women who were attended to in our hospital during the first month of the epidemic in Spain.

MATERIAL AND METHODS

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Data were collected from the first 60 pregnant women with COVID-19 who were treated at Puerta de Hierro University Hospital Madrid, Spain from March 14th to April 14th, 2020.

Demographic variables collected were maternal age, type of exposure, gestational age, parity and information on the course of the pregnancy. In addition, the following clinical data were extracted from the medical records: symptoms, pneumonia diagnosis, CURB65 (Confusion, Urea, Respiratory rate, Blood pressure, 65 years) score for pneumonia severity (shown in figure 1), hospital admission, respiratory co-infections, type of delivery and treatment.

All patients were seen in the Obstetrics Emergency Room either due to showing clinical symptoms (e.g., fever, cough and respiratory distress) or because they were in labor. COVID-19 diagnosis was confirmed by a quantitative reverse transcription PCR (RT-PCR) test for SARS-CoV-2 on nasopharyngeal swabs. All COVID-19 patients were classified as: a) Stage I, or early infection phase, if the patient was asymptomatic or if symptoms were fever, cough, diarrhea, or headache. B) Stage II, or lung disease phase, if patient presented dyspnea; c) Stage III, or hyperinflammatory phase, if sepsis, shock, or cardiac failure were diagnosed.

Laboratory tests included a complete blood count, complete coagulation, renal and liver function tests, D-dimer, CRP, lactate dehydrogenase (LDH), creatine kinase, troponin I, ferritin and interleukin 6 levels. Moreover, patients with symptoms underwent chest radiography, obstetric ultrasound, fetal heart rate monitoring (if >23 weeks pregnant). For those prescribed hydroxychloroquine, an electrocardiogram (normal QTc interval=460) was also performed.

Hospital admission

Pregnant COVID-19 women were admitted to the hospital either because they were in labor or due to presenting symptoms or signs of disease complications (e.g., persistent fever, dyspnea, radiological diagnosis of pneumonia or oxygen saturations below 95%). The severity of pneumonia was classified following a radiography-based score in which each of the five lung lobes was assessed for degree of involvement and classified as normal: 0%, mild pneumonia: 1% to 25%, moderate pneumonia: 26% to 50%, or severe pneumonia: >50%.[15]

Treatment for pregnant COVID-19 women

The protocols implemented at our hospital were:

a) Mainly symptomatic treatment for asymptomatic patients: rest at home and 1 gr. of Paracetamol every 8 hours, as needed, for fever or general discomfort; b) Protocol 1 for pregnant women with

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comorbidities and/or symptoms of upper respiratory tract infection; c) Protocol 2 for patients with mild pneumonia; d) Protocol 3 for patients with severe pneumonia and acute respiratory distress syndrome or for patients with poor clinical progression. The description of protocols 1, 2 and 3 are shown in figure 2. Protocols 2 and 3 required hospital admission and oxygen therapy.

Childbirth

Vaginal delivery or cesarean section were indicated according to the protocols of the Spanish Society of Gynecology and Obstetrics. Additionally, caesarean sections were indicated for maternal benefit if a severe health disorder, such as Severe Acute Respiratory Syndrome, appeared. Delivery care was performed by obstetricians and all delivery staff followed the precautions and recommendations on infection prevention and control. All newborns were tested for SARS-CoV-2 in the first 2 hours after delivery by quantitative RT-PCR on samples from the respiratory tract (nasopharyngeal swab). In cases where the newborns had respiratory distress syndrome, the SARS-CoV-2 test was repeated 24 hours later. Samples of six placentas were also tested for SARS-CoV-2 by quantitative RT-PCR.

Statistical analyses

Medians and ranges of all the variables were calculated and an analysis of variance (Kruskal-Wallis test) was performed to compare the medians of the laboratory parameters obtained on the first and last days of assessment. The Fisher´s exact test and the relative risk were used to evaluate associations between variables and the health status of pregnant COVID-19 patients; p-values less than 0.05 were considered significant.

A correspondence analysis was used to explore associations between CRP, D-Dimer, and LDH levels, and lymphopenia and the progression of the disease in patients with mild, moderate and severe pneumonia. This analysis was also used to establish the value of the goodness-of-fit statistics and assign order to unordered variables. The statistical analysis was performed using R version 3.6.3 software (R Core Team, 2020).

Ethical approval

Approval was given by the hospital's Research Ethics Committee (reference number: PI 78/20; date of approval: April 14, 2020) and an Informed Consent was signed by all patients.

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RESULTS

A total of 60 pregnant women were confirmed to have COVID-19 by an RT-PCR test (cobas® SARS-CoV-2 by Roche Diagnostics) for SARS-CoV-2 on nasopharyngeal swabs. The demographic characteristics of the study population are shown in table 1. More than one-third of patients were infected at home or by relatives. The median maternal age was 34 years (range, 22-43 years). The median gestational age was 32 weeks (range, 5-41 weeks).

During the first 5 days of illness, patients were asymptomatic but already contagious. Subsequently, 25% remained asymptomatic, 70% developed mild or moderate symptoms, and 5% severe to critical symptoms. The most common symptoms among our patients were fever and cough. Dyspnea was present in 17 of them (37.8%). Hospital admissions were necessary in 41 patients (68.3%): 18 due to COVID-19 complications and 23 for deliveries. A total of 10 patients needed oxygen support (10%), via nasal prongs for 8 patients and high flow oxygen mask with reservoir bag for 2 patients. Eighteen patients (30%) were diagnosed with pneumonia based on a chest radiograph. Three patients were evaluated by the intensive care unit (ICU), and one of them required ICU admission. During this period there were no maternal deaths. Clinical findings are shown in table 2.

The most common laboratory findings in pregnant COVID-19 women are summarized in tables 3 and 4. In the study, the median of CRP and D-dimer levels, and the neutrophil/lymphocyte ratio (NLR) were elevated. The cut-off value for each variable in severe pneumonia were: CRP >60 mg/L, D-dimer >1,9 µg/ml, and lymphocytes <0,9 x10E3/microL. Of all patients with persisting and severe symptoms, three (5%) had high ferritin and interleukin 6 levels. None of the patients were diagnosed with renal or cardiac failure.

Oxygen saturation, liver function, CRP and LDH levels, lymphopenia, NLR, dimer-D levels, and thrombocytopenia were correlated with the worsening of COVID-19 disease; results are shown in tables 3 and 4.

Symptomatic treatment was required for 39 patients (65%), and experimental treatment was administered in 21 patients (35%); protocols and distributions of treatments are summarized in figure 2 and table 2. In addition, 5 patients required antibiotics due to respiratory co-infections (*Pneumococcus*, *Haemophilus influenza*, *Methicillin-Resistant Staphylococcus aureus*, *Mycoplasma pneumoniae*), and 25 patients were treated with low molecular weight heparin (LMWH) for thromboprophylaxis.

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During the study period, twenty-three women with COVID-19 delivered in our Hospital; five of them had cesarean section (one due to maternal respiratory failure at 34^{+2} weeks gestation with uterine activity and breech presentation, two for non-progression of labor, one for induction failure and one due to hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome) and 18 had vaginal deliveries. Placental tissue from 6 cases was sent to the Microbiology Unit; SARS-CoV-2 was not identified in any of the placental samples. Two of the 23 deliveries were preterm. The clinical course in the puerperium was uncomplicated for 22 patients; only one patient (a HELLP syndrome) required ICU admission. The twenty-three newborns tested negative for SARS-CoV-2 by RT-PCR nasopharyngeal swabs. Twenty-one of the 23 neonates were breastfed and two of them needed admission to the Neonatal Intensive Care Unit: one because of a respiratory distress syndrome and the other due to hemolytic anemia.

The statistical analysis demonstrated that continuous decreases of NLR was shown to be the most sensitive marker for disease improvement (relative risk: 6.65; 95% CI: 4.1-5.9). Furthermore, a multivariate analysis with a correspondence analysis revealed an association between CRP and D-dimer levels with severe pneumonia ($p<0.000$). Likewise, elevated neutrophil counts are associated with severe pneumonia ($p =0.024$).

DISCUSSION

According to the evolution of our patients, we describe COVID-19 as a three phase disease:

The early infection phase is a viral response phase, where the most common symptoms are fever, cough, diarrhea, or headache. Seventy percent of our patients were asymptomatic or had mild symptoms at the time of diagnosis; they only received symptomatic treatment and the disease did not progress further in any of these cases. Lymphopenia (50%) and thrombocytopenia (25%) were observed in early stages of disease, and close to 60% of patients had an increased CRP (table 4).

In the lung disease phase, SARS-CoV-2 can cause massive damage to the liver and renal tissues which results from an excessive release of cytokines that, in turn, induces a severe pro-inflammatory response in the lungs which frequently causes dyspnea and hypoxemia. In our study, 38% of our patients showed dyspnea and 40% of symptomatic patients presented with pneumonia. Moderate or severe pro-inflammatory response in the lung accounts for 15% of them (table 2). Transitory hepatic disorder was present in 25-50% of pregnant women with pneumonia (table 3).

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During the observation period, lymphopenia (40%), and increased NLR (85%), CRP (75%), and D-dimer (95%) levels were present in pregnant COVID-19 patients, which is consistent with the published medical data.[12-14] Moreover our study demonstrated NLR decrease as a potential marker of patient improvement.

The hyperinflammatory phase occurs when an excessive immune and inflammatory response arises. As we previously stated above, critical status in pregnant COVID-19 women accounts for 5%.[14] interleukin 6 and ferritin levels, were significantly elevated during the critical infection phase. However, no patients developed hepatic, renal or cardiac failure in our cohort. In general terms, respiratory viral infections increase the risk of bacterial infections leading to a more severe respiratory disease. In our cohort, the most severe cases had neutrophilia and a concurrent bacterial sepsis (one with pneumococcus and one with methicillin-resistant staphylococcus aureus) or were associated with HELLP syndrome. For this reason, we believe that pregnant COVID-19 women with pneumonia should be investigated for the early diagnosis and treatment of possible bacterial respiratory co-infections.

Data from China suggested that the clinical course of SARS CoV-2 infected pregnant women is similar to that of the general population.[16-18] In our experience, the normal course of pregnancy was altered in 18% of COVID-19 positive women. In our cohort, 5% had preeclampsia, 5% fetal growth restriction, 5% preterm birth and 3% had coagulopathy.

The incidence of preeclampsia in non-COVID-19 pregnant population is reported to be 3.4% to 4.6%.[19,20] One of our patients developed a HELLP syndrome and two had preeclampsia. There could be an association between COVID-19 and preeclampsia as it has been described that SARS-CoV-2 uses the angiotensin-converting enzyme 2 receptor for cell entry.[21]

Coronavirus infection is often complicated by coagulopathy, which is associated with a high mortality rate. Additionally, high D-dimer levels is a sign of coagulopathy and indicates poor prognosis.[22-24] As in non-pregnant women, D-dimer may be increased in pregnant and puerperal women with coronavirus infection. In fact, our study showed that D-dimer increases in those patients with severe clinical features. Given the increased thromboembolic risk during pregnancy and puerperium, consideration should be given to prescribing thromboprophylaxis to these patients. Based on our experience and several observations,[25] we have developed a protocol to initiate low molecular weight heparin at prophylactic dose for at least 10 days after delivery. We recommend increasing low molecular weight heparin to therapeutic dose for 6 weeks after delivery, in those patients with higher thromboembolic risk.

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Finally, the scarce evidence published until now suggests the lack of vertical transmission, as SARS-CoV-2 was not detected in the placental, amniotic fluid or neonate samples immediately after birth.[26-28] However, caesarean sections were performed in almost all previously published cases.[14] At our hospital, 18 of 23 COVID-19 positive women had a vaginal delivery and the delivery care followed the World Health Organization recommendations. In all of our 60 cases, neonates tested negative, irrespective of the mode of delivery. Therefore, we hypothesize that there is no vertical transmission through the birth canal.

The Breastfeeding Committee at Puerta de Hierro University Hospital approved breastfeeding of newborns by mothers with COVID-19, provided that adequate protection measures were taken and World Health Organization and United Nations International Children's Emergency Fund recommendations were followed.[29,30] We did not diagnose COVID-19 any of the breast-fed infants.

The present study has several limitations resulting from its retrospective design and small sample size. This study was carried out in the first 4 weeks of an epidemic that has caused devastating consequences in our country. The scarcity of diagnostic tests, limited knowledge about the disease, the limited access to antiretroviral drugs, restricted hospital capacity for admission and intensive care could have affected the clinical outcomes. Therefore, our results should be interpreted with caution and their generalizability may be limited.

CONCLUSION

In 70% of our cases, the clinical course of COVID-19 in pregnant women was mild. Only 30% of patients had pneumonia, 5% of which developed a critical condition. High CRP and D-dimer levels correlated with severe pneumonia, while an NLR decrease suggested a favorable outcome for pregnant women. Vaginal delivery appears to be safe, as 78% of our patients had vaginal delivery and none of the newborns were infected.

References:

1. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579:270-273.

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Accepted Article

2. World Health Organization. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). Jan 30, 2020. https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the- international-health-regulations-(2005)-emergency-committee- regarding-the-outbreak-of-novel-coronavirus-(2019-ncov) (accessed Feb 29, 2020).
3.Wuhan Municipal Health Commission. Report on current pneumonia epidemic situation in the city. (In Chinese.) Dec 31, 2019. http://wjw.wuhan.gov.cn/front/web/ showDetail/2019123108989 (accessed Feb 29, 2020).
4.https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/situacionActual.htm. (accessed March 21, 2020).
5. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, re- plication, and pathogenesis. J Med Virol. 2020; 92:418-423.
6. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727-733.
7. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;382:1199-1207.
8. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579:265-269.
9. Wang W, Tang J, Wei F. Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. J Med Virol. 2020;92:441-447.
10. Wu P, Hao X, Lau EHY, et al. Real-time tentative assessment of the epidemiological characteristics of novel coronavirus infections in Wuhan, China, as at 22 January 2020. Euro Surveill. 2020;25(3).
11. Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). Biosci Trends. 2020;16;14:69-71.
12. Liang H, Acharya G. Novel corona virus disease (COVID-19) in pregnancy: what clinical recommendations to follow? Acta Obstet Gynecol Scand. 2020;99:439-442.
13. Poon LC, Yang H, Kapur A, et al. Global interim guidance on coronavirus disease 2019 (COVID-19) during pregnancy and puerperium from FIGO and allied partners: Information for healthcare professionals. Int J Gynaecol Obstet. 2020 Apr 4. doi: 10.1002/ijgo.13156. [Epub ahead of print]

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14. Zaigham M, Andersson O. Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies. Acta Obstet Gynecol Scand. 2020 Apr 7. doi: 10.1111/aogs.13867. [Epub ahead of print].
15. Wong HYF, Lam HYS, Fong AH et al. Frequency and Distribution of Chest Radiographic Findings in COVID-19 Positive Patients. 2019 Mar 27:201160. doi: 10.1148/radiol.2020201160. [Epub ahead of print].
16. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 2020;395:809-815.
17. Yu N, Li W, Kang Q, et al. Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study. Lancet Infect Dis. 2020;20:559-564.
18. Liu D, Li L, Wu X, et al. Pregnancy and Perinatal Outcomes of Women With Coronavirus Disease (COVID-19) Pneumonia: A Preliminary Analysis. AJR Am J Roentgenol. 2020 Mar 18:1-6. doi: 10.2214/AJR.20.23072. [Epub ahead of print].
19. Abalos E, Cuesta C, Grosso AL, et al. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2013;170:1-7.
20. Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. BMJ. 2013;347:f6564.
21. Gorbalenya AE, Baker SC, Baric RS, et al. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020;5:536-544.
22. Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020 2020;18:844-847.
23. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507-513.
24. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.
25. Thachil J. The versatile heparin in COVID-19. J Thromb Haemost. 2020;18:1020-1022.

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26. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 2020;7;395:809-815.
27. Li Y, Zhao R, Zheng S, et al. Lack of Vertical Transmission of Severe Acute Respiratory Syndrome Coronavirus 2, China. Emerg Infect Dis. 2020 Jun 17;26(6). doi: 10.3201/eid2606.200287. [Epub ahead of print].
28. Schwartz DA. An Analysis of 38 Pregnant Women with COVID-19, Their Newborn Infants, and Maternal-Fetal Transmission of SARS-CoV-2: Maternal Coronavirus Infections and Pregnancy Outcomes. Arch Pathol Lab Med. 2020 Mar 17. doi: 10.5858/arpa.2020-0901-SA. [Epub ahead of print].
29. WHO, UNICEF (2018) Protecting, promoting, and supporting breastfeeding in facilities providing maternity and newborn services: the revised Baby-friendly Hospital Initiative 2018 Implementation guidance. Department of Nutrition for Health and Development World Health Organization. World Health Organization, Geneva, Switzerland.
30. UNICEF (2019) https://www.unicef.org/stories/novel-coronavirus-outbreak-what-parents-should-know. Accessed on March 24th, 2020

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Legends

Table 1. Demographic characteristics of COVID 19 pregnant women.

Abbreviations: N: Number of patients. %: Percentage. yr: year. FGR: fetal growth restriction. FSGA: fetal small for gestational age. RPB: risk of preterm birth. DVT: deep venous thrombosis

Table 2. Descriptive analyses of clinical findings.

Abbreviation: N: number of patients, %: Percentage.

Table 3. Changes in laboratory test variables in COVID-19 pregnant women during the course of disease.

Abbreviation: N: number of patients, %: Percentage, P: statistical significance. SatO2: Oxygen saturation. AST: aspartate aminotransferase. ALT: alanine aminotransferase. CRP: C-reactive protein, LDH: lactate dehydrogenase. NRL: neutrophils/ lymphocytes ratio.

Table 4. Distribution of laboratory test variables in COVID-19 pregnant women.

Abbreviation: N: number of patients, %: Percentage, P: statistical significance. SatO2: Oxygen saturation. AST: aspartate aminotransferase. ALT: alanine aminotransferase. CRP: C-reactive protein, LDH: lactate dehydrogenase. NRL: neutrophils/ lymphocytes ratio.

Figure 1. Pneumonia risk score CURB-65. BUN, blood urea nitrogen; ICU, intensive care unit.

Figure 2. Flowchart of COVID 19 pregnant women. N: Number of patients. %: percentage.

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Table 1. Demographics characteristics of COVID 19 pregnant women

	Overall	N (%)
Maternal age	60	
< 30yr		11 (18.3%)
30-34 yr		24 (40.0%)
35-40 yr		22 (36.7%)
> 40 yr		3 (5.0%)
Exposure type	60	
Infected at household or by relatives		21 (35.0%)
Infected at workplace		6 (10.0%)
• Healthcare professionals		• 4
• Other professions		• 2
Mixed: family/workplace		1 (1.7%)
Unknown		32 (53.3%)
Gestational age	60	
1st trimester (1-12 weeks)		10 (16.7%)
2nd trimester (13-26 weeks)		16 (26.7%)
3rd trimester (27-41 weeks)		34 (56.6%)
Parity	60	
Primiparous		27 (45.0%)
Multiparous		33 (55.0%)
Plurality	60	
Singleton		60 (100%)
Multiple		0 (0%)
Pregnancy follow up	60	
Normal		49 (81.7%)
Abnormal		11 (18.3%)
• FGR/ FSGA		• 3
• RPB		• 3
• Preeclampsia		• 3
• DVT		• 2

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Abbreviations: N= number; %: percentage; yr: year; FGR: fetal growth restriction (fetal weight <3rd percentile for gestational age); FSGA: fetal small for gestational age (fetal weight <10th percentile for gestational age); RPB: risk of preterm birth, DVT: deep venous thrombosis

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Table 2. Descriptive analyses of clinical findings

	Overall	
Symptoms	60	**N (%)**
Asymptomatic COVID-19		15 (25.0%)
Symptomatic COVID-19		45 (75.0%)
• Fever		• 34 (75.5%)
• Cough		• 34 (75.5%)
• Dyspnea		• 17 (37.8%)
COVID-19 stages	60	**N (%)**
Stage I or early infection phase		42 (70.0%)
Stage II or lung disease phase		15 (25.0%)
Stage III or hyperinflammatory phase		3 (5.0%)
CURB65 scale		
0		57 (95.0%)
1		3 (5.0%)
≥2		0 (0%)
COVID-19 pregnant patients	60	**N (%)**
Without pneumonia		42 (70.0%)
With pneumonia		18 (30.0%)
• Mild		• 9 (50.0%)
• Moderate		• 7 (38.9%)
• Severe		• 2 (11.1%)
• Respiratory co-infection		• 5 (27.8%)
Hospital admissions	41	**Median (range)**
COVID-19 length of stay (days). N=18		3 (1-13)
Delivery length of stay (days). N=23		3 (1-9)
Delivery	60	**N (%)**
Overall		23 (38.3%)
• Spontaneous vaginal delivery		• 14 (60.9%)
• Instrumental delivery		• 4 (17.4%)
• Caesarean section		• 5 (21.7%)
Premature delivery		2 (8.7%)

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Vertical transmission to newborn		0 (0%)
Treatment	60	**N (%)**
Symptomatic		39 (65.0%)
Hydroxychloroquine		10 (16.7%)
Hydroxychloroquine+lopinavir+ritonavir		3 (5.0%)
Hydroxychloroquine+darunavir+ritonavir		3 (5.0%)
Hydroxychloroquine+darunavir+ritonavir+tocilizumab		2 (3.3%)
Hydroxychloroquine+darunavir+cobicistat		3 (5.0%)

Abbreviations: N= number; %: percentage; yr: year.

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Lab variables (measure, normal range)	Total		1st day at Hospital		Last day at Hospital		
	Median	Range	Median	Range	Median	Range	p
SatO2 (<95%)	96	87-99	97	93-99	95	91-100	0.325
AST (U/L, 6-40)	27	14-86	25	13-58	25	14-54	0.876
ALT (U/L, 6-40)	15.8	8-108	16	8-37	17	7-124	0.305
CRP (mg/L, 0.1 - 10)	17.8	0.9-147.4	15.9	0.9-118.7	17	1.8-147.4	0.873
LDH (U/L, 120 - 246)	188.5	134-437	178.5	134-345	189	120-352	0.708
Lymphocytes (x10E3/microL, 1.2 - 4)	1.3	0.4-2.5	1.2	0.6-2.4	1.5	0.9-2.4	0.118
Neutrophils (x10E3/microL, 1.5 -7.5)	5.6	1.2-10.3	5.4	2.5-8.2	4.2	1.2-5.9	0.205
N/L ratio (<3)	4.6	1.3-14.4	4.5	2.4-10.2	2.6	1.3-5.7	**0.009**
D-dimer (µg/ml, 0.1 - 0.5)	1.0	0.2-7.8	1.0	0.2-1.9	1.3	0.3-2.3	0.834
Platelets (x10E3/microL, 150- 400)	218	100-466	193.5	109-320	206	147-382	0.217
Lab variables (measure, normal range)	**Mild pneumonia**		**Moderate pneumonia**		**Severe pneumonia**		
	Median	**Range**	**Median**	**Range**	**Median**	**Range**	**P**
SatO2 (<95%)	97	91-100	96	85-99	95	87-99	0.063
AST (U/L, 6-40)	36.5	25-62	34.3	14-83	41	20-86	0.972
ALT (U/L, 6-40)	29.5	15-49	26	8-108	24	13-75	0.747
CRP (mg/L, 0.1 - 10)	23.0	4.5-44.6	23.7	3.6-118.7	60	1.8-147.4	0.435
LDH (U/L, 120 - 246)	180	154-437	210.3	154-379	225.5	161-297	0.256
Lymphocytes (x10E3/microL, 1.2 - 4)	1.2	0.6-2	1.4	0.4-1.8	0.9	0.5-2.4	0.434
Neutrophils (x10E3/microL, 1.5 -7.5)	3.9	2.4-6.9	5.6	1.4-10.1	6.2	2.4-10.3	**0.024**
N/L ratio (<3)	3.7	1.3-10.2	5.2	1.7-14.4	6.8	2.5-13.9	0.056
D-dimer (µg/ml, 0.1 - 0.5)	0.9	0.5-2.2	0.9	0.4-1.8	1.9	0.4-7.8	0.841
Platelets (x10E3/microL, 150- 400)	196	164-288	233	100-466	240	132-321	0.507

Table 3. Changes in laboratory test variables in COVID-19 pregnant women during the course of disease

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Abbreviation: N: number of patients, %: Percentage, P: statistical significance. SatO2: Oxygen saturation. AST: Aspartate Aminotransferase. ALT: Alanine Aminotransferase. CRP: C-reactive protein, LDH: lactate dehydrogenase. NRL: neutrophils/ lymphocytes ratio.

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Table 4. Distribution of laboratory test variables in COVID-19 pregnant women

Lab variables (measure, normal range)	Total		1st day at Hospital		Last day at Hospital		
	N	%	N	%	N	%	p
SatO2 (<95%)	5/19	26	1/15	7	3/14	21	0.336
↑AST (U/L, 6-40)	4/20	20	1/17	6	3/15	20	0.445
↑ALT (U/L, 6-40)	1/20	5	0/17	0	2/15	13	0.371
↑CRP (mg/L, 0.1 - 10)	15/20	75	10/17	59	10/13	77	0.575
↑LDH (U/L, 120 - 246)	4/20	20	2/14	14	3/14	21	1
↓Lymphocytes (x10E3/microL, 1.2 - 4)	8/20	40	10/20	50	4/14	29	0.535
↑Neutrophils (x10E3/microL, 1.5 -7.5)	2/20	10	3/20	15	0/14	0	0.420
↑N/L ratio (<3)	17/20	85	19/20	95	4/14	29	**2.69e-05**
↑D-dimer (µg/ml, 0.1 - 0.5)	18/19	95	15/16	96	9/12	75	0.281
↓Platelets (x10E3/microL, 150- 400)	3/20	15	5/20	25	0/14	0	0.239
Lab variables (measure, normal range)	**Mild pneumonia**		**Moderate pneumonia**		**Severe pneumonia**		
	N	**%**	**N**	**%**	**N**	**%**	**P**
SatO2 (<95%)	0/4	0	1/6	17	1/2	50	0.409
↑AST (U/L, 6-40)	1/4	25	2/6	33	1/2	50	1
↑ALT (U/L, 6-40)	0/4	0	1/6	17	0/2	0	1
↑CRP (mg/L, 0.1 - 10)	3/4	75	5/6	83	2/2	100	1
↑LDH (U/L, 120 - 246)	0/4	0	2/6	33	1/2	50	0.346
↓Lymphocytes (x10E3/microL, 1.2 - 4)	2/4	50	2/6	33	2/2	100	0.481
↑Neutrophils (x10E3/microL, 1.5 -7.5)	0/4	0	2/6	33	0/2	0	0.636
↑N/L ratio (<3)	2/4	50	6/6	100	2/2	100	0.106
↑D-dimer (µg/ml, 0.1 - 0.5)	4/4	100	6/6	100	2/2	100	1
↓Platelets (x10E3/microL, 150- 400)	0/4	0	1/6	17	0/2	0	1

Abbreviation: N: number of patients, %: Percentage, P: statistical significance. SatO2: Oxygen saturation. AST: Aspartate Aminotransferase. ALT: Alanine Aminotransferase. CRP: C-reactive protein, LDH: lactate dehydrogenase. NRL: neutrophils/ lymphocytes ratio.

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Figure 1. Pneumonia risk score CURB-65

	Assign 0 or 1 point	Score
C	Confusion	**1**
U	Urea BUN>19 mg/dL	**1**
R	Respiratory rate ≥30/minutes	**1**
B	Blood pressure Systolic ≤90 mmHg or Diastolic ≤60 mmHg	**1**
65 yr	Age ≥65years	**1**
	The CURB-65 scores range from 0 to 5	

CURB-65 Score	Risk Group	30-day mortality	Management
0 -1	1	1.5%	Home
2	2	9.2%	Likely to need admission
≥ 3	3	22%	Inpatient admission with consideration for ICU

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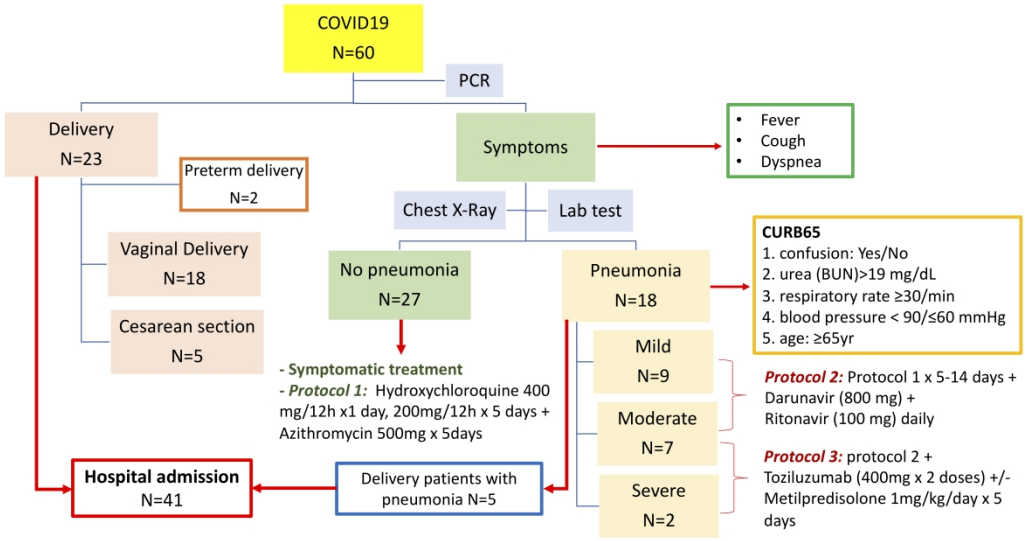
Figure 2. Flowchart of COVID 19 pregnant women



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