Maternal and Neonatal Outcome of the Pregnant With COVID-19 in Istanbul, Turkey: A Single-Center, Descriptive Study

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Abstract

Objective To determine maternal and neonatal outcomes in pregnant women with COVID-19 Design Retrospective, descriptive study Setting A single-center managing pregnant women with COVID-19 Population or Sample Third-trimester pregnant women with a diagnosis of COVID-19 Methods A retrospective, single-center, descriptive study Main Outcome Measures The maternal and neonatal results of COVID-19 pregnant women were evaluated by looking at the following parameters: the concentrations of D-dimer, complete blood count, ferritin, C-reactive protein, lymphocytes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), neonatal umbilical blood gas analyzes, real-time RT-PCR tests, lung CT imaging, admission to (neonatal) intensive care unit. Results In the third trimester, 40 pregnant women with COVID-19 were included. The most common complaint was cough (50%). The most common symptom that accompanied cough was fever and shortness of breath. Thirty-four patients delivered by cesarean and 6 patients delivered vaginally. Two patients were taken to the intensive care unit because of respiratory distress. There were no maternal and fetal deaths. The patients were hospitalized for an average of 5 days. One patient was followed up without treatment, while all other patients were given hydroxychloroquine. In addition, azithromycin, oseltamivir, or lopinavir/ritonavir were added to some patients in addition to hydroxychloroquine. Conclusions The clinical features of pregnant women with COVID-19 are comparable compared to non-pregnant adults. Long-term results and comparative studies are needed in this regard.

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Abstract

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To determine maternal and neonatal outcomes in pregnant women with COVID-19

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Retrospective, descriptive study

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Third-trimester pregnant women with a diagnosis of COVID-19

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The maternal and neonatal results of COVID-19 pregnant women were evaluated by looking at the following parameters: the concentrations of D-dimer, complete blood count, ferritin, C-reactive protein, lymphocytes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), neonatal umbilical blood gas analyzes, real-time RT-PCR tests, lung CT imaging, admission to (neonatal) intensive care unit.

Results

In the third trimester, 40 pregnant women with COVID-19 were included. The most common complaint was cough (50%). The most common symptom that accompanied cough was fever and shortness of breath. Thirty-four patients delivered by the caesarean section (c-section) and 6 patients delivered vaginally. Two patients were taken to the intensive care unit because of respiratory distress. There were no maternal and fetal deaths. The patients were hospitalized for an average of 5 days. One patient was followed up without treatment, while all other patients were given hydroxychloroquine. In addition, azithromycin, oseltamivir, or lopinavir/ritonavir were added to some patients in addition to hydroxychloroquine.

Conclusions

The clinical features of pregnant women with COVID-19 are comparable compared to non-pregnant adults. Long-term results and comparative studies are needed in this regard.

Pregnancy, COVID-19, Maternal Outcome, Neonatal Outcome

Introduction

The coronavirus caused a number of unknown pneumonia cases that showing clinically similar to viral pneumonia in Wuhan, a city in the Hubei Province of China, in December 2019 [1]. On January 30, 2020, the World Health Organization (WHO) announced that the new coronavirus (2019-nCoV) was a public health emergency of international concern (PHEIC). The virus spread rapidly all over the world and the number of cases began to increase in the other countries in February 2020 [2]. The first case in our country was announced on March 11, 2020. Until this date, the number of cases detected in the world was 125900, but now (2 June) is 6.378M [3]. Currently, knowledge on the epidemiology and clinical features of pneumonia in pregnancy caused by COVID-19 is limited. For this reason, nowadays, there is a need for all information about COVID-19 in pregnancy.

Effective obstetric therapy is required in these pregnant women and is key to optimizing prognosis for both mother and child. Care should be individualized in determining the time of delivery, evaluating the c-section indications, preparing the delivery room to prevent infection, choosing the type of anesthesia and managing the newborn. Birth and treatment experiences are limited for pregnant women who have had the disease in the last 3 months [4, 5].

In our study, we aim to define the epidemiological, clinical, laboratory and radiological features, maternal and neonatal outcomes and treatment of pregnant women confirmed to have SARS-CoV-2 infection.

Methods

This retrospective, single-center study was conducted at Istanbul Kanuni Sultan Suleyman Training and Research Hospital, Turkey, between April to May 2020. The study protocol was approved by the institution's Ethics Committee and registered to ClinicalTrials.gov (NCT04337320).

Our study criteria included pregnant women between 18–45 years old with a history of COVID-19 positive PCR result. Patients with COVID-19 positive PCR who used systemic drugs as well as women with other endocrine and/or autoimmune disorders, pregnant women who had underlying lung disease were excluded from the study.

The demographic data of participants including age, gravidity, parity, gestational week at admission were recorded. Blood samples from each patient were obtained to determine the concentrations of D-dimer, complete blood count, ferritin, C-reactive protein (CRP), lymphocytes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). At the same time, neonatal umbilical blood gas analyzes were also examined. We evaluated real-time RT-PCR tests from upper respiratory tract obtained from all patients at admission. We also requested lung CT from all patients, except for 4 patients who did not wish to have any imaging tests. Six of the fourty patients had normal vaginal delivery (NVD), others were delivered by the c-section and all newborn infants were admitted to the neonatology department for seperation from the mother and also for blood and PCR tests.

The primary outcome of our study was to compare maternal and neonatal results in pregnant women with a history of COVID-19 positive PCR result.

Data analysis was performed using the SPSS version 20 for Windows (SPSS Inc., Chicago, IL). Continuous variables were expressed using means with standard deviations and categorical variables were given as number (%).

Patient Involvement

There were no patient or public participation in this study.

Funding

Results

Forty pregnant women with COVID-19 were included in the study. The demographic information of the patients are shown in Table 1. Two patients had a history of chronic disease (Type 2 Diabetes Mellitus and Hypothyroidism).

Most of the patients presented with cough complaints (50%). The most common symptoms accompanied by cough were fever and shortness of breath. A significant number of patients were asymptomatic (42.5%). While 15 patients needed nasal oxygen support during their hospitalization, 2 of our patients were hospitalized in the intensive care unit (ICU) due to serious respiratory problems. We divided the patients into groups according to stages of CT findings. We detected 10 patients with mild involvement, 11 patients with moderate involvement and 8 patients with severe involvement. Lung CT finding and the clinical features of the patients are summarized in Table 2.

Laboratory findings of the pregnant at admission such as complete blood count, coagulation tests, liver function tests, ferritin and CRP were examined (Table 3).

Thirty-four of the patients had a c-section and six of them had a vaginal delivery. A patient with a previous c-section had severe AST (1560 U / L) and ALT (435 U / L) levels. Oxygen saturation under oxygen support was 94%. She had tachycardia (130 beats per minute) and shortness of breath. When she was 36 weeks of pregnancy, the decision was made by cesarean delivery. Four babies needed neonatal intensive care unit (NICU). Obstetric and neonatal characteristics are demonstrated in Table 4.

Forty-five percent of the patients received only hydroxychloroquine treatment. One patient was followed up without treatment. Low molecular weight heparin treatment (LMWH) was started for all patients. Patients with a D-dimer value above 2 mg / L were administered LMWH twice daily. Treatment options are shown in Table 5.

Discussion

Main Findings

The disease spread in our country in April and May. So far, 165,555 cases and 4585 deaths have been reported in our country[6]. This study is a descriptive study reporting the maternal and neonatal results of pregnant women with COVID-19 from a centre with an annual birth rate of over 10,000.

This article reports the maternal and fetal results of 3rd trimester pregnant women who applied with COVID-19 in a tertiary center working as a pandemic hospital. 85% of patients gave birth by c-section. There was no maternal-fetal mortality and serious morbidity. Cough was the most common symptom, while 42.5% of patients were asymptomatic. As a general treatment approach of the country, the treatment was started by providing hydroxychloroquine within a short time after diagnosis.

Strengths and Limitations

The most important advantage of the study is that it is single-centered and covers 40 patients. Similarly, the number of patients was generally kept lower in other articles planned. Nevertheless, this study has some limitations. All patients included are in the third trimester, it is still unknown how the fetuses of pregnant women whom infected with COVID-19 in the first and second trimesters will be affected. More studies are needed for the maternal and neonatal long-term results of the pandemic.

Interpretation

Coronaviruses (CoV) are a large family of viruses that cause a variety of diseases, from the common cold to more serious diseases such as the Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). Human beings can also be infected by inhalation of droplets scattered from the respiratory tract of the sick individuals or by contact with the surfaces contaminated with these aeroceles[7]. Eighteen of our patients (45%) had a contact with people whom had a history of the disease. Current evidence suggests that the severity of disease among pregnant women after COVID-19 infection is

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similar to non-pregnant adult COVID-19 cases, and there is no data showing that infection with COVID-19 during pregnancy has a negative effect on the fetus. So far, there is no evidence that vertical transmission from mother to baby during pregnancy [8]·In our study, no vertical transition was detected as no Infant had positive PCR test.

In 2002-2003, there was a high maternal mortality rate in the SARS-CoV-1 outbreak [9]· However, there has not been a similar situation in SARS-CoV-2 yet. However, more studies are needed on this subject. Looking at the current studies, it seems difficult to make clear comments. [10-12]. In Turkey, as of June 2, the overall mortality rate of the disease is 2.76 %, and there are no published articles showing maternal mortality rates in pregnant women with COVID-19 [6]. Similarly, no maternal and fetal death has been observed in our hospital too.

In terms of clinical findings in patients, the common symptoms at baseline were cough, fever, and difficulty breathing, and the rate of asymptomatic patients was 22 [13, 14]· Similar to current studies, laboratory tests were observed as low lymphocyte count, increased CRP and D-dimer [15, 16].

The relatively high mortality of COVID-19 is making people feel anxious. Most of the women had c-section in our study similar to the literature[17]· The most common c-section indication was maternal request. This was followed by difficulty breathing and anxiety.

Lung CT findings are important for the diagnosis of pneumonia in pregnant women with COVID-19. In patients who had mild involvement in CT, multiple patchy frosted glass areas are peripherally located rather than parenchyma, and lesions increased as the disease progresses. According to the study conducted by Li M et al., extensive pulmonary consolidations are observed in cases of severe involvement, "white lungs" may appear on the radiogram, but pleural effusion is rare[18]·

In treatment, hydroxychloroquine is usually used in combination with a second-generation macrolide. There is not enough data to know if it has a role in treatment, but it is widely used. It can also cause QT prolongation and ventricular arrhythmias, which may pose a certain risk for critical patients [19]· Among the 40 patients we studied, no cardiac side effects related to drug use were observed. In addition, heparin has been suggested to be added into treatment by some specialized consensus due to the risk of disseminated intravascular coagulation and venous thromboembolism. Heparin treatment has been related to well prognosis, mostly in severe COVID-19 cases with high D-dimer concentrations [20]. Lopinavir, another treatment option, is a protease inhibitor used to treat HIV in combination with ritonavir. In one of the randomized study with 199 patients by Bin Cao et al., 99 of these patients were evaluated in the group receiving lopinavir-ritonavir and 100 in the standard care group. According to this study, it was observed that there was no additional benefit of lopinavir-ritonavir treatment beyond standard care in adult patients diagnosed with heavy Covid-19 [21]·Oseltamivir is an approved neuraminidase inhibitor for the treatment of influenza. Since the epidemic in China occurred during the peak season of influenza, oseltamivir was added to the treatment of patients. In fact, this agent has no role in the treatment of COVID-19 after influenza has been excluded [22]· We applied LMWH and hydroxychloroquine to pregnant women as standard treatment. We observed one of our patients without treatment because she was asymptomatic and laboratory values were normal. Initially, we added oseltamivir to the treatment of 7 patients due to the seasonal period. We used lopinavir/ritonavir treatment in patients who needed oxygen therapy and had severe involvement findings on lung CT. We have created our treatment algorithm according to the "COVID-19 guide", which is updated regularly by our health ministry since the disease first appeared in our country. Changes in treatments arise from this. [23]·

Conclusion

According to our experience, the clinical features of pregnant women with COVID-19 in the third trimester are similar compared to non-pregnant adults. According to our study, no vertical transition was observed. Maternal and fetal results seem favourable to non-COVID-19 pregnant women. Long-term results and comparative studies are needed.

Acknowledgments

Contribution to authorship

IP, MAT, PYB and MC thought of the idea of working. MAT, PYB, AB and OK identified women and collected relevant patient data. Data analysis and interpretation were made by AA and SYS. IP, MAT and PYB wrote the first draft and was later critically reviewed by all authors. All authors have read and approved the last article.

REFERENCES

1. Hui DS, E IA, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020;91:264-6.

2. Organization WH. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. Internet] World Health Organization. 2020.

3. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) [Available from: https://coronavirus.jhu.edu/map.html.

4. Yu N, Li W, Kang Q, Xiong Z, Wang S, Lin X, 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(5):559-64.

5. Qi H, Luo X, Zheng Y, Zhang H, Li J, Zou L, et al. Safe delivery for pregnancies affected by COVID-19. Bjog. 2020.

6. Ministry TRH. Current Situation in Turkey 2020 [updated June 2, 2020. Available from: https://covid19.saglik.gov.tr.

7. Prevention CCfDCa. How to Protect Yourself & Others [Available from: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html.

8. Panahi L, Amiri M, Pouy S. Risks of Novel Coronavirus Disease (COVID-19) in Pregnancy; a Narrative Review. Arch Acad Emerg Med. 2020;8(1):e34.

9. Wong SF, Chow KM, Leung TN, Ng WF, Ng TK, Shek CC, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. American journal of obstetrics and gynecology. 2004;191(1):292-7.

10. 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.

11. Thornton JG. COVID-19 in pregnancy. Bjog. 2020.

12. Zaigham M, Andersson O. Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies. Acta Obstet Gynecol Scand. 2020.

13. Mullins E, Evans D, Viner RM, O'Brien P, Morris E. Coronavirus in pregnancy and delivery: rapid review. Ultrasound Obstet Gynecol. 2020;55(5):586-92.

14. Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, et al. Outcome of Coronavirus spectrum infections (SARS, MERS, COVID 1 -19) during pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM. 2020;2(2):100107.

15. Rasmussen SA, Smulian JC, Lednicky JA, Wen TS, Jamieson DJ. Coronavirus Disease 2019 (COVID-19) and pregnancy: what obstetricians need to know. Am J Obstet Gynecol. 2020;222(5):415-26.

16. Ferrazzi E, Frigerio L, Savasi V, Vergani P, Prefumo F, Barresi S, et al. Vaginal delivery in SARS-CoV-2-infected pregnant women in Northern Italy: a retrospective analysis. Bjog. 2020.

17. Della Gatta AN, Rizzo R, Pilu G, Simonazzi G. Coronavirus disease 2019 during pregnancy: a systematic review of reported cases. Am J Obstet Gynecol. 2020.

18. Li M, Lei P, Zeng B, Li Z, Yu P, Fan B, et al. Coronavirus Disease (COVID-19): Spectrum of CT Findings and Temporal Progression of the Disease. Acad Radiol. 2020;27(5):603-8.

19. Barlow A, Landolf KM, Barlow B, Yeung SYA, Heavner JJ, Claassen CW, et al. Review of Emerging Pharmacotherapy for the Treatment of Coronavirus Disease 2019. Pharmacotherapy. 2020;40(5):416-37.

20. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. Journal of Thrombosis and Haemostasis. 2020;18(5):1094-9.

21. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. New England Journal of Medicine. 2020.

22. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. Jama. 2020.

23. Ministry TRH. COVID-19 (SARS-CoV-2 INFECTION) (Scientific Board Study)

ANTICYTOCIN-ANTI-INFLAMMATORY TREATMENTS, COAGULOPATHY MANAGEMENT Ankara2020 [updated June 1,2020. Available from: https://covid19bilgi.saglik.gov.tr/depo/rehberler/covid-19-rehberi/COVID-19_REHBERI_ANTISITOKIN-ANTI_INFLAMATUAR_TEDAVILER_KOAGU-LOPATI_YONETIMI.pdf.

Table 1 Demographic characteristics

Demographic characteristics	Study Group (n=40)	Min- Max	%95 CI
Age	27.7 ± 6.6	18-45	25.6 - 29.9
Gravidity	2.5 ± 1.5	1-8	2.0 - 2.9
Parity	1.2 ± 1.4	0-6	0.7 - 1.7
Gestational week at admission	37 ± 2.7	29-41	36.1 - 37.9
Previous C-section (n,%)	9 (22,5%)		
Chronic disease Type 2 DM (n,%) Hypothyroidism Previous contact with Covid-19 patient	1 (2.5%) 1 (2.5%) 18 (45%)		

Table 2 Clinical features of the patients

Clinical features of the patients	Study Group (n=40)	Min- Max	%95 CI
Symptom (n,%) Asymptomatic Fever Cough Shortness of breath Fatigue Anosmia	17 (42.5%) 10 (25%) 20 (50%) 10 (25%) 2 (5%) 2 (5%)		
Body tempurature (°C) Heart rate (bpm) Oxygen saturation	36.5 ± 0.7 94.7 ± 15.1 96.2 ± 2.8	35.5-39 69-136 88-100	36.3 - 36.7 89.8 - 99.5 95.3-97.1
Systolic blood pressure (mmHg)	114.9 ± 12.8	90-142	110.8-119
Diastolic blood pressure (mmHg) Need for oxygen teraphy Need for ICU (n,%) Lung CT findings Refused investigation No involvement Mild involvement Moderate involvement Severe involvement	70.7 ± 9.9 19 (47.5%) 2 (5%) 4 (10%) 7 (17.5%) 10 (25%) 11 (27.5%) 8 (20%)	50-89	67.5-74

Table 3 Laboratory findings at admission

Laboratory findings at admission	Mean ± SD (n=40)	Min- Max	%95 CI
Hemoglobin (gr/dl) Hematocrit (%) Platelet count (10^3/µL) D-dimer (mg/L)	11.4±1.4 34.3±3.5 222±70 3.1±2.7	8.4-15.3 25.7-45.2 102-468 1-14.9	11-12 33.2-35.4 200-245 2-3.9
Ferritin (ng/mL) AST(U/L)	50.8±57 67.2±242	9.4-355 12-1560	32-69.4 -10.3-145
ALT (U/L) CRP mg/L Lymphocyte count (10^3/µL)	32.3±69 31.4±52 1.8±1.5	5-435 0.7±292.6 0.5±8.5	10.2-54.4 14.6-48.3 1.3-2.3

Table 4 Obstetric and neonatal characteristics

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Obstetric and neonatal characteristics	Study Group (n=40)	Min- Max	%95 CI
Delivery route (n,%) C-section Vaginal C-section indications (n,%) Multiple pregnancy Previous C-section Maternal hypoxia Maternal request Malpresentation	34 (85%) 6 (15%) 2 (5,8%) 9 (26,4%) 3 (8,8%) 15 (44,1%) 2 (5,8%)		
Fetal distress Premature birth (n,%)	3 (7,5%) 15 (37,5%)		
Birth weight (gram) 5th minute APGAR score Umblical cord pH Need for NICU Positive neonatal PCR test	2955 ± 656 8.8 ± 0.6 7.38 4 (10%) 0	1255-4000 6-9 7.2-7.4	2745- 3165 8.6-9 7.37-7.39

Table 5 Treatement Options

Treatement Options	Study Group (n=40)	Min- Max
None- observation (n,%) LMWH Hydroxychloroquine (n,%) Hydroxychloroquine +azithromycin (n,%) Hydroxy-chloroquine+azithromycin +oseltamivir (n,%) Hydroxy-chloroquine+lopinavir/ritonavir (n,%)	1 (2.5%) 40 (100%) 18 (45%) 7 (17.5%) 7 (17.5%) 4 (10%)	
Hydroxychloroquine+azithromycin +lopinavir/ritonavir (n,%) Duration of hospitalization (days)	3 (7.5%) 5,4 ± 2,5	2-12