The Impact of Coronavirus Disease-19 on Pregnancy Outcomes, A Case Series

Bilge CETINKAYA DEMIR[1], Ozge ALBAYRAK[1], Kiper ASLAN[1]

Bursa, Türkiye

ABSTRACT

OBJECTIVE: To investigate the impact of Corona Virus Disease 19 (COVID-19) infection on pregnancy outcomes.

STUDY DESIGN: This retrospective study was conducted at a tertiary university hospital between the years of October 2020-October 2021. All the pregnant women with COVID-19 diagnoses were enrolled in the study during this period. Demographic parameters, a history of Favipiravir use, COVID-19 symptoms, treatment approaches, hospitalization, intensive care unit admission, and obstetric and neonatal outcomes were recorded.

RESULTS: A total of 92 patients were enrolled in the study. The mean age was 30+5 years. Forty-seven of the patients were asymptomatic (51%). The most common symptoms were respectively; fatigue (37.8%), fever (27.6%), dyspnea (22%), cough (17.8%), headache (11%), anosmia (4.4%), hyperemesis (4.4%), diarrhea (2.2%). There were 20 patients (21.7%) who were hospitalized. Eight of these women (8.6%) required intensive care unit admission due to COVID pneumonia-related acute respiratory distress syndrome. Five of the patients treated in the intensive care unit died due to respiratory failure. Two patients had a miscarriage before the 20th week. There were four stillbirths. The gestational weeks at which fetal death occurred were 24, 26, 28, and 38 weeks of gestation. There were 19 patients with a history of favipiravir use. There was not any other congenital abnormality due to Favipiravir usage.

CONCLUSION: Our study showed that COVID-19 disease has similar symptoms in pregnant women to non-pregnant women, according to the literature data. However, COVID-19 infection increases the rates of pregnancy complications and maternal mortality.

Keywords: Corona virusdisease, COVID-19, Favipiravir, Pregnancy

Gynecol Obstet Reprod Med 2023;29(1):30-35

Introduction

Since the first case of Coronavirus Disease 19 (COVID-19) was reported in Wuhan City, China (1), there have been over five million deaths with nearly 500 million cases due to COVID-19 infection (2). The COVID-19 pandemic is one of the most devastating pandemics of our times regarding this actual number. Although it has been over three years, health providers still could not find an exact treatment for the disease. Symptomatic treatments and vaccines have been developed, but the curative treatment is still waiting to be explored. Beyond the treatment, there are too many unknowns about COVID-19. The disease can react differently in different patient populations, such as pregnant women. Pregnant women may be risky of developing more severe conditions after infection due to physiological changes in the immune and cardiopulmonary systems during pregnancy (3). Small case series was published at the first stages of the pandemic and those studies reported increased fatality and more severe complications during pregnancy (4-6). However, COVID-19 pneumonia in pregnant women has been reported to be similar to that in non-pregnant women (7,8). The exact relationship between COVID-19 and pregnancy is not very clear. Furthermore, there is still no evidence of vertical transmission of COVID-19 (9). Therefore, the intrauterine and neonatal effects of the disease due to maternal infection are also unclear.

The present study aimed to investigate the association between COVID-19 and pregnancy. We studied the maternal

[1] *Bursa Uludag University Faculty of Medicine Dept. of Obstetrics and Gynecology Bursa, Türkiye*

Address of Correspondence: *Kiper Aslan*
Bursa Uludag University Faculty of Medicine, Dept. of Ob&Gyn
16285 Bursa, Türkiye
kiperaslan@yahoo.com.tr

Submitted for Publication: 26.05.2022 Revised for Publication: 27.05.2022
Accepted for Publication: 30.08.2022 Online Published: 16.09.2022

ORCID IDs of the authors: BCD: 0000-0001-6845-9991
OA: 0000-0002-1113-4296 KA: 0000-0002-9277-7735

Quick Response Code:	Access this article online
	Website: www.gorm.com.tr e- mail: info@gorm.com.tr
	DOI:10.21613/GORM.2022.1319

How to cite this article: *Cetinkaya Demir B. Albayrak O. Aslan K. The Impact of Coronavirus Disease-19 on Pregnancy Outcomes, A Case Series. Gynecol Obstet Reprod Med. 2023;(29)1:30-35*

and neonatal outcomes of COVID-19-positive pregnant women.

Material and Method

Study Design, Ethical Approval: This retrospective study was conducted at Bursa Uludag University School of Medicine, Dept. of Obstetrics and Gynecology. The study protocol was approved by Bursa Uludag University Faculty of Medicine, Clinical Trials Ethical Committee with the number; 2022-1/10.

Patient Selection: The study period was from 1 October 2020-1 October 2021. The women who were admitted to the perinatology clinic were investigated. Pregnant women whose COVID-19 PCR test was positive and who had a history of favipiravir usage during pregnancy or before pregnancy (<8 weeks) were included in the study. Since the study was conducted in a perinatology clinic, a control group consisting of non-pregnant women with COVID-19 could not be formed.

Interventions and Statistical Analysis: Demographic parameters, obstetric history, maternal and fetal risk factors, gestational age at the COVID-19 diagnosis, symptoms, treatment approaches, favipiravir usage, the need for hospitalization or intensive care unit (ICU), and obstetric & neonatal outcomes of all patients were recorded from the electronic database. To investigate whether there is any adverse effect of COVID-19 disease on the placenta, the placentas of all patients with stillbirth were evaluated by the pathology department.

Depending on the distribution, continuous variables are defined as mean ± standard deviation (SD) or median (25^{th}-75^{th} percentile). Categorical variables are defined as percentages.

Results

Eighty-nine patients with COVID-19 PCR positive test and three with Favipiravir usage due to COVID before pregnancy (<8 weeks) were included in the study. The obstetric outcomes of the six patients were missing. Four patients were diagnosed in the first trimester, and the other two were diagnosed at the 34^{th} and 35^{th} weeks of pregnancy. They gave birth elsewhere due to their clinical well-being. Therefore, a total of 86 patients' records were included in the analysis (Figure 1)

Five patients were health providers (one pediatrist-intubated, one internal medicine resident, one clinic staff, one operation room staff, and one wife of the operation room staff). The incidence of COVID-19 in health providers was found as 5.4%.

The mean age was 30+5 yrs. The median gestational week at COVID-19 diagnosis was 14 (25-75 Percentiles; 5-25) weeks. Forty-seven of the patients were asymptomatic (51%) (Figure 2). The most common symptoms were respectively; fatigue (37.8%), fever (27.6), dyspnea (22%), cough (17.8%), headache (11%), anosmia (4.4%), hyperemesis (4.4%), diarrhea (2.2%) (Figure 3).

There were 20 hospitalized patients (21.7%). Eight of

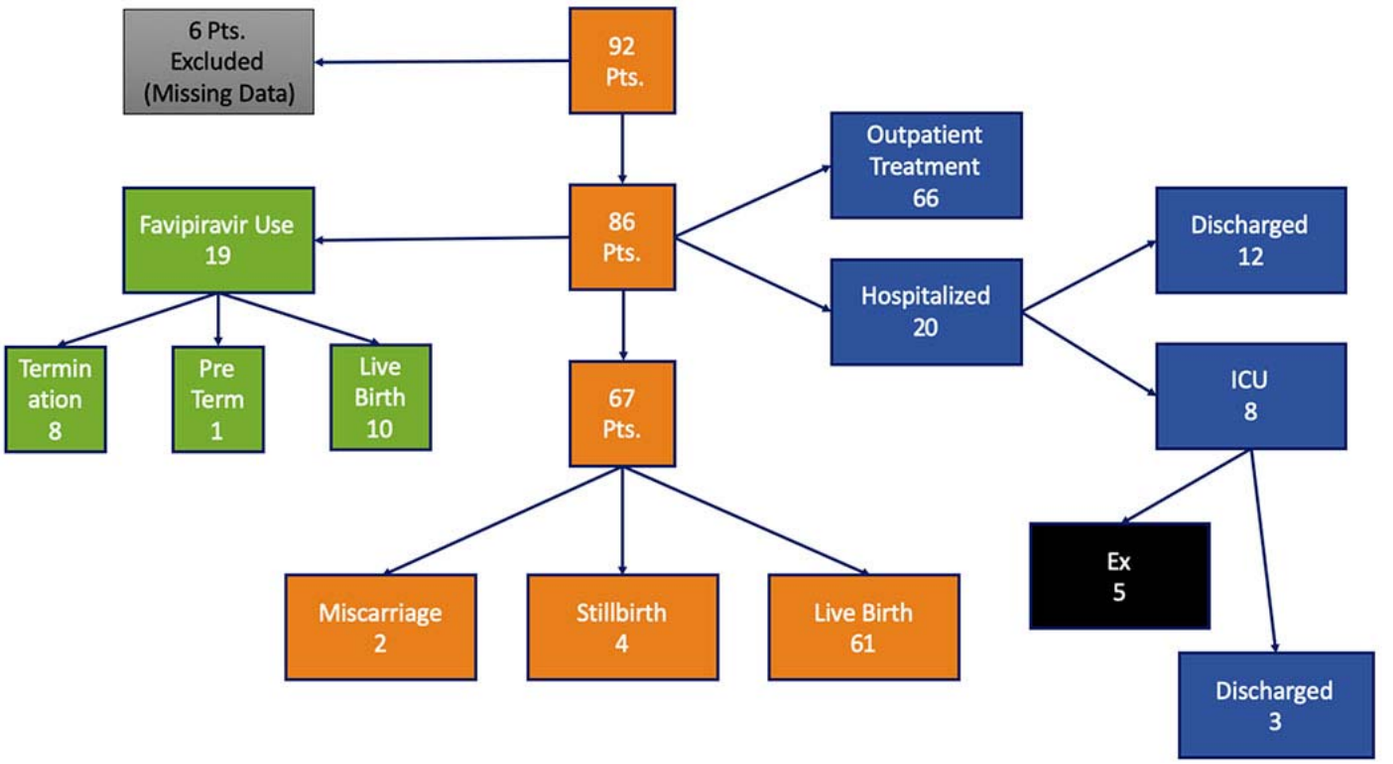

Figure 1: *Patient flowchart*

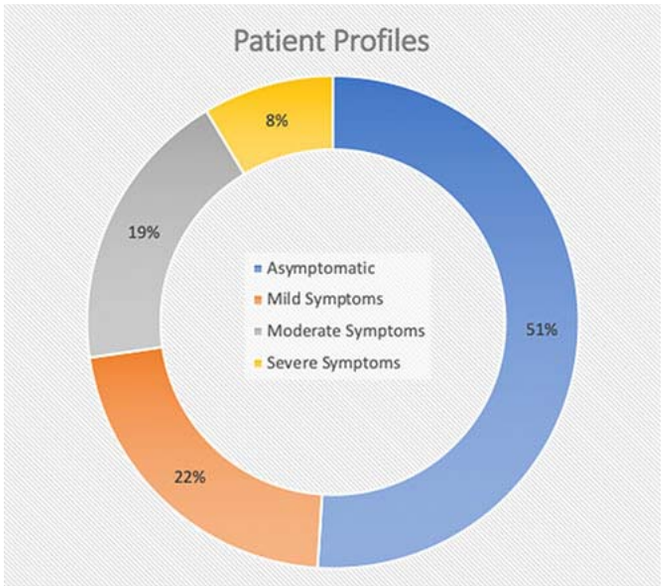

Figure 2: *Patient profiles*

these women (8.6%) required ICU admission due to COVID pneumonia-related acute respiratory distress syndrome. Five

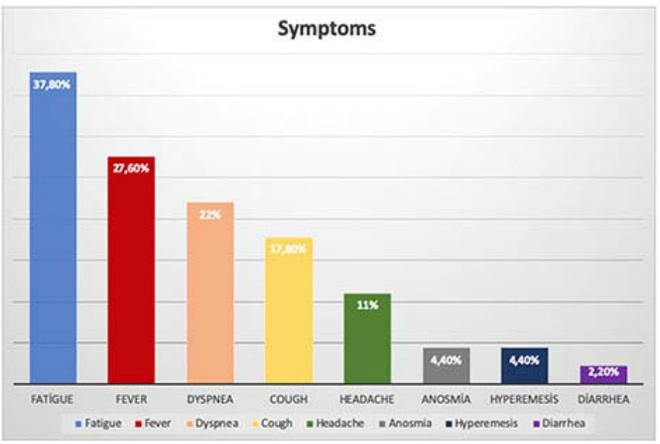

Figure 3: *COVID-19 disease symptoms in pregnant women*

patients in the ICU died due to respiratory failure. One of these patients had 20 weeks of pregnancy. Therefore, we did not plan the birth, but the others had viable pregnancies. Cesarean section (CS) was performed for these patients after intubation. Details are given in table I.

Table I: *Maternal and neonatal outcomes of the patients who required ICU admission*

Age	Gravida	Parity	Symptom	Gestational Week at COVID-19 Diagnosis	Treatments	Intubation	Maternal Outcome	Birth Week	Birth Indication	Way of the birth	Fetal Weight	APGAR Score
28	2	1	Fatigue	25	Favipiravir Remdesivir Meropenem LMWH	Yes	Ex (Myocarditis)	28	Fetal Demise	Vaginal Birth	600	0
23	4	3	Fatigue Dyspnea	34	Ritonavir Lopinavir LMWH	Yes	Ex (Respiratory Failure)	34	Previous CS	CS	2290	8-9
30	2	1	Dyspnea Fatigue Fever	28	Remdesivir Prednisolon e LMWH	Yes	Discharged	28	Fetal Distress	CS	1260	1-4-5-6 Intubated
36	1	0	Dyspnea Fatigue Fever	25	Remdesivir Prednisilone LMWH	Yes	Discharged (ECMO for 3 Months)	25	Maternal Indication	CS	845	1-5-7 Intubated
36	1	0	Dyspnea Fever	24	Remdesivir Prednisilone LMWH	Yes	Discharged at 27th pregnancy week	38	Elective	CS	3500	9-10
23	1	0	Dyspnea Fatigue	27	Steroid Remdesivir Ceftriaxone Ritonavir Anakinra	Yes	Ex (Respiratory Failure)	28	Fetal Distress	CS	1070	1-4-5-5 Intubated
31	4	3	Dyspnea Fatigue	19	Lonipavir Prednisolon e LMWH	Yes	Ex (Respiratory Failure)	21	Preterm Birth	Vaginal Birth	400	-
26	2	1	Dyspnea Fatigue	26	Lonipavir Steroid LMWH Ceftriaxone	Yes	Ex (Respiratory Failure)	28	Twin/ Preterm Birth	CS	1080/ 1035	7-8 /7-8

Nineteen patients had favipiravir usage (preconceptionally eight weeks or earl pregnancy <8 weeks). Eight of these patients underwent pregnancy termination due to favipiravir's teratogenicity. One of the patients with ongoing pregnancy after favipiravir usage had preterm labor due to PPROM (21st pregnancy week). The remaining 10 pregnancies resulted in live births. The routine audiometry test was abnormal in one of the newborns. There was another neonate with unexplained neonatal seizures & abnormal electroencephalogram (EEG). There was not any other congenital abnormality due to favipiravir usage.

Two patients had a miscarriage before the 20th week. There were four stillbirths. These patients had no favipiravir usage. The gestational weeks at which fetal death occurred were 24th, 26th, 28th, and 38th weeks. Pathological examination of placentas taken from these patients was reported as placental infarct. Details are given in table II.

Mean birth week was 354+5 weeks, mean birth weight was 2934+898 gr. Fifty-six patients gave birth by CS and 15 patients by vaginal delivery.

The median APGAR1 score was 7 (25-75 Percentiles; 8-9), and the median APGAR5 was 8 (25-75 Percentiles; 8-9).

All the neonates were tested for COVID-19 by PCR test on the first day, and none of the tests was positive.

Discussion

This study presented the pregnancy outcomes of COVID-19 positive-women. While 51% of the women were asymptomatic, 21.7% required hospitalization, and 8.6% needed ICU admission. The maternal mortality rate due to COVID-19 was 5.4%. The overall mortality rate is approximately 1.2% according to the World Health Organization (WHO) Coronavirus database (2). These results show that pregnancy complicates the progress of the COVID-19 disease. Furthermore, the maternal mortality rate is nearly 30 times higher than the healthy population. The increased mortality rate of COVID-19-positive pregnancies is thought to be related to physiological changes due to pregnancy conditions. A widespread multinational study by Villar et al. showed that COVID-19 in pregnancy is associated with consistent and substantial increases in severe maternal morbidity and mortality (10). Another reason for the high mortality rate in our study may be related to the fact that our hospital is a referral center. The main reason for our deaths was respiratory failure due to COVID-19 pneumonia, except for one patient who died because of myocarditis (Table II).

Beyond the increased maternal mortality, there is enough evidence about the relationship between adverse pregnancy outcomes and COVID-19 (4). We demonstrated relatively high miscarriage (4.3%) and stillbirth (4.3%) than the healthy population. These results are also similar to the previously published studies about COVID-19 pregnancies. Kumari et al. reported a stillbirth rate of 2.7% (11), and another study investigating the pregnancy results of low-income countries found a 2.8% stillbirth rate during the COVID-19 pandemic (12). A prospective comparative study demonstrated the 5.1% stillbirth rate in COVID-19-infected mothers (13). The possible etiology for fetal loss is mainly related to the effects of the virus on the fetoplacental unit, notably with coagulopathy (14,15). In our study, pathological examination of placentas taken from patients with stillbirth was reported as infarct. Therefore, the exact reason for the fetal loss is probably placental coagulopathy due to COVID-19 infection.

There was a total of 71 live births in our study. The

Table II: *Demographic parameters of the patients with fetal demise*

No	Age (years)	Risk Factors	Gestational Week at COVID-19 Diagnosis	Estimated Week of Fetal Demise	Notes
1	24	Hydrops Fetalis	28	29	The etiology of hydrops fetalis could not be determined in the pregnancy follow-up, it was found to be positive for COVID-19 during the routine checks after fetal death.
2	36	Trisomy 21	14	38	The fetus had serious cardiac malformations due to Trisomy 21. The patient had COVID-19 infection at the 14th week of pregnancy and fetal death occurred at the 38th week.
3	26	Chronic Hypertension	15	24	The patient had regular visits during pregnancy without hypertension until COVID-19 infection. During the infection, fetal growth restriction and superimposed pre-eclampsia developed. Pathologic investigation of the placenta resulted in an infarct.
4	37	IVF Twin Pregnancy	25	27	The patient had COVID-19 pneumonia and pulmonary embolism. One of the fetuses died in utero. CS was performed and APGAR 6-7 940 gr healthy fetus was born. Pathologic investigation of the placenta resulted in infarct, bleeding, and chorioamnionitis.

preterm delivery rate in our study was 27%. The main reason was preterm labor. A meta-analysis of COVID-19 pregnancies reported a preterm birth rate of 29.7% in case reports and 16% in observational studies (16).

The cesarean rate in our study was 75%. The most common indications for CS were previous CS - almost half, fetal distress 19%, and malpresentation 11%. At the beginning of the pandemic, there was a trend toward CS for all suspected infectious mothers to avoid intrapartum transmission (17). Novel case series show high rates of CS than expected numbers (over 80%) (17,18). Our results are consistent with the published data.

None of the fetuses had a positive COVID-PCR test. These results support that COVID-19 infection has no vertical transmission during pregnancy. There is still no evidence of vertical transmission. A systematic review that included 43 articles with 1300 neonates born from pregnant women confirmed for COVID-19 reported that only 93 (7%) of the newborns' tests were positive, which may be due to perinatal or postnatal transmission (19).

Another issue about COVID-19 and pregnancy is favipiravir usage. Favipiravir is an antiviral drug that is one of the treatment options for COVID-19 (21). Favipiravir use has been shown to increase congenital malformations and fetal loss in animal studies (22). Therefore, it is contraindicated to use it preconceptionally and during pregnancy. Moreover, it has adverse effects on sperm (23). There were 19 women with a history of favipiravir use (preconceptionally or during pregnancy). Eight of these patients decided to terminate the pregnancy in the first trimester due to the high risk of teratogenicity. Other women (12/19) who wished to continue pregnancy were followed up.

One patient had preterm labor due to amniotic fluid leakage at the 21st gestational week. The only observed congenital malformations were ventriculomegaly and nasal bone hypoplasia. The ventriculomegaly spontaneously regressed before birth. We performed chorionic villus sampling for the fetus with nasal bone hypoplasia, and the result was reported as 46 XX. The patient gave a healthy 3460 gr girl by CS. There were two neonatal abnormalities; one fetus had an abnormal audiometry test, and one had unexplained seizures with abnormal EEG. We do not know whether these abnormalities are related to favipiravir use. A novel publication that assessed favipiravir and pregnancy outcomes showed that favipiravir is unlikely to be a major human teratogen (24). The data is still limited for a well-grounded assessment of favipiravir. United States Food and Drug Administration (FDA) has only approved Remdesivir as an antiviral drug for COVID-19 (25).

Our study has some limitations; Firstly, we tried to compare our results with the published literature data, lack of a control group limits the interpretation of our results. Secondly, since our hospital is a referral center, the high number of risky patients may have affected the results.

Conclusion

In this study, we reported the outcomes of COVID-19-positive pregnancies. Our results showed that COVID-19 has similar symptoms in pregnant women to non-pregnant women according to the literature data. However, COVID-19 infection increases fetal loss rates (miscarriage or stillbirth), preterm birth, CS, and, maternal mortality.

Declarations

Ethics Approval and Consent for Using Data: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Bursa Uludag University (2022-1/10).

Funding: The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing Interests: The authors declare that they have no competing interests.

Author" Contributions: All authors contributed to the study's conception and design. BCD designed and reviewed the study. Material preparation, data collection, and analysis were performed by OA. The first draft of the manuscript was written by KA and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Availability of data and materials: The data underlying this article can be shared on reasonable request to the corresponding author.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8): 727-33. Doi: 10.1056/NEJMoa2001017. PMID:31978 945, PMCID: PMC7092803.
2. WHO COVID-19 Dashboard. Geneva: World Health Organization, 2020. Available online: https://covid19.who.int/(last cited: [13.04.2022]).
3. Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. Emerg Infect Dis. 2006;12(11): 1638-43. Doi: 10.3201/eid1211.060152. PMID: 17283 611, PMCID: PMC3372330.
4. Wang CL, Liu YY, Wu CH, Wang CY, Wang CH, Long CY. Impact of COVID-19 on pregnancy. Int J Med Sci. 2021;18(3):763-7. Doi: 10.7150/ijms.49923. PMID: 334 37211, PMCID: PMC7797535.
5. Favre G, Pomar L, Musso D, Baud D. 2019-nCoV epidemic: what about pregnancies? Lancet. 2020;395 (10224):e40. Doi: 10.1016/S0140-6736(20)30311-1.

PMID: 32035511, PMCID: PMC7133555.

6. Schwartz DA, Graham AL. Potential maternal and infant outcomes from (Wuhan) Coronavirus 2019-nCoV infecting pregnant women: Lessons from SARS, MERS, and other Human Coronavirus infections Viruses. 2020;12 (2): 194. Doi: 10.3390/v12020194. PMID: 32050 635, PMCID: PMC7077337
7. Wenling Y, Junchao Q, Xiao Z, Ouyang S. Pregnancy and COVID-19: management and challenges. Rev Inst Med Trop Sao Paulo. 2020;62:e62. Doi: 10.1590/s1678-9946202062062. PMID: 32876296, PMCID: PMC74580 76.
8. Di Toro F, Gjoka M, Di Lorenzo G, De Santo D, De Seta F, Maso G, et al. Impact of COVID-19 on maternal and neonatal outcomes: a systematic review and meta-analysis. Clin Microbiol Infect. 2021;27(1):36-46. Doi: 10. 1016/j.cmi.2020.10.007. PMID: 33148440, PMCID: PMC7605748.
9. Poblete AC, Bancalari MA. Transmisión vertical de COVID-19. ¿Qué dice la evidencia? [Vertical transmission of Covid - 19. What does the evidence say?]. Andes Pediatr. 2021;92(5):790-8. Spanish. Doi: 10.32641/andespediatr.v92i5.3488. PMID: 35319589.
10. Villar J, Ariff S, Gunier RB, Thiruvengadam R, Rauch S, Kholin A, et al. Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: The INTERCOVID Multinational Cohort Study. JAMA Pediatr. 2021;175(8):817-26. Doi: 10.1001/ jamapediatrics. 2021.1050. PMID: 33885740, PMCID: PMC8063132.
11. Kumari K, Yadav R, Mittra S, Kumar A, Singh J, Bajpai PK, et al. pregnancy consequences and vertical transmission potential of SARS-CoV-2 infection: seeking answers from a preliminary observation. J Reprod Infertil. 2021;22(2):144-7. Doi: 10.18502/jri.v22i2.5804. PMID: 34041012, PMCID: PMC8143008.
12. Naqvi S, Naqvi F, Saleem S, Thorsten VR, Figueroa L, Mazariegos M, et al. Health Care in Pregnancy During the COVID-19 Pandemic and Pregnancy Outcomes in Six Low-and-Middle-Income Countries: Evidence from a Prospective, Observational Registry of the Global Network for Women's and Children's Health. BJOG. 2022;129(8):1298-307. Doi: 10.1111/1471-0528.17175. PMID: 35377514, PMCID: PMC9111322.
13. Hcini N, Maamri F, Picone O, Carod JF, Lambert V, Mathieu M, et al. Maternal, fetal and neonatal outcomes of large series of SARS-CoV-2 positive pregnancies in peripartum period: A single-center prospective comparative study. Eur J Obstet Gynecol Reprod Biol. 2021;257:11-8. Doi: 10.1016/j.ejogrb.2020.11.068. PMID: 33310656, PMCID: PMC7705341.
14. Miesbach W, Makris M. COVID-19: Coagulopathy, risk of thrombosis, and the rationale for anticoagulation. Clin Appl Thromb Hemost. 2020;26:1076029620938149. Doi: 10.1177/ 1076029620938149. PMID: 32677459, PMCID: PMC7370334.
15. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020;135 (23): 2033-40. Doi: 10.1182/blood.2020006000. PMID: 3233 9221, PMCID: PMC7273827.
16. Bellos I, Pandita A, Panza R. Maternal and perinatal outcomes in pregnant women infected by SARS-CoV-2: A meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2021; 256:194-204. Doi: 10.1016/ j.ejogrb.2020.11.038. PMID: 33246205, PMCID: PMC7664337.
17. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, 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(10226):809-15. Doi: 10.1016/S0140-6736(20) 30360-3 PMID: 32151335, PMCID: PMC7159281.
18. Ghosh MD, Datta MR, Singh V, Choudhary A. Analysis of pregnant women recovered from antenatal SARS-COV-2 infection: an observational study. Cureus. 2022; 14(2):e22094. Doi: 10.7759/cureus.22094. PMID: 35295 360, PMCID: PMC8917808.
19. Gupta V, Yadav Y, Sharma R, Mishra M, Ambedkar D, Gupta V. Maternal and Perinatal Outcomes of Hospitalized COVID-19 Positive Pregnant Women. Cureus. 2022;14(2):e21817. Doi: 10.7759/cureus. 21817. PMID: 35261836, PMCID: PMC8894144.
20. Wake AD. Intrauterine vertical transmission of SARSCoV-2 infection among confirmed cases of pregnant women: "A Double Burden for the Pregnant Women"-a systematic review. Glob Pediatr Health. 2022;9: 2333 794X221089765. Doi: 10.1177/2333794X2 21089765. PMID: 35386229, PMCID: PMC8977699.
21. Sood S, Bhatia GK, Seth P, Kumar P, Kaur J, Gupta V, et al. Efficacy and safety of new and emerging drugs for COVID-19: Favipiravir and Dexamethasone. Curr Pharmacol Rep. 2021;7(2):49-54. Doi: 10.1007/s40495-021-00253-w. PMID: 33619447, PMCID: PMC7889701.
22. Joshi S, Parkar J, Ansari A, Vora A, Talwar D, Tiwaskar M, et al. Role of favipiravir in the treatment of COVID-19. Int J Infect Dis. 2021;102:501-8. Doi: 10.1016/j.ijid. 2020.10.069. PMID: 33130203, PMCID: PMC7831863.
23. Nagata T, Lefor AK, Hasegawa M, Ishii M. Favipiravir: a new medication for the Ebola virus disease pandemic. Disaster Med Public Health Prep. 2015;9(1):79-81. Doi: 10.1017/dmp.2014.151. PMID: 25544306.
24. Tırmıkçıoğlu Z. Favipiravir exposure and pregnancy outcome of COVID-19 patients. Eur J Obstet Gynecol Reprod Biol. 2022;268:110-5. Doi: 10.1016/j.ejogrb. 2021.12.001. PMID: 34902747, PMCID: PMC 864 7391.
25. National Institutes of Health. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines [cited 2021 August 10] Available from https://covid19treatmentguideli nes. nih.gov/