Journal of
Kerman University of Medical Sciences

https://jkmu.kmu.ac.ir
10.34172/jkmu.2024.26
Vol. 31, No. 4, 2024, 158-164

Original Article

Open Access
Publish Free

Pregnancy Implication Related to the COVID-19 Pandemic

Masoumeh Baghalishahi[1], Shahriar Dabiri[2], Shahrzad Sadat Eftekharvaghefi[3,4,5], Vida Mirzaie[6], Hossein Bonakchi[7], Mona Saheli[1*]

[1]Department of Anatomical Sciences, and Pathology and Stem Cell Research Centre, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran
[2]Department of Pathology, Pathology and Stem Cell Research Center, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran
[3]Pathology and Stem Cell Research Centre, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran
[4]Department of Basic Sciences, Faculty of Medicine, Kerman Branch, Islamic Azad University, Kerman, Iran
[5]Department of Physiology and Pharmacology, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran
[6]Department of Anatomical Sciences, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran
[7]Department of Biostatistics, Faculty of Paramedical Science, Shahid Beheshti University of Medical Sciences, Tehran, Iran

*Corresponding Author: Mona Saheli, Email: saheli.mona@gmail.com

Abstract

Background: COVID-19 that is caused by severe acute respiratory syndrome coronavirus 2, is being classified as a pandemic and has influenced all aspects of human life. Although some groups, such as pregnant women, are at higher risk, the information on COVID-19 effects on pregnancy has remained limited yet.

Methods: This study aimed to evaluate the effects of the COVID-19 pandemic on the fetal mortality rate (FMR). The delivery status of all asymptomatic pregnant women hospitalized in 5 hospitals located in Kerman city, Iran, were checked three months before and three months during this pandemic.

Results: According to the results, compared to the non-COVID-19, the COVID-19 period increased FMR with an odds ratio of 1.40 (95% CI: 1.14-1.72), meaning that the coronavirus could increase the risk of fetal death by 40%.

Conclusion: The evidence suggests that more careful and accurate screening approaches are needed for asymptomatic pregnant individuals to avoid risks to the fetus and mother.

Keywords: Fetal death, COVID-19, Coronavirus, Coronavirus disease, Pandemic, Pregnant women

Citation: Baghalishahi M, Dabiri S, Eftekharvaghefi SS, Mirzaie V, Bonakchi H, Saheli M. Pregnancy implication related to the COVID-19 pandemic. *Journal of Kerman University of Medical Sciences*. 2024;31(4):158–164. doi: 10.34172/jkmu.2024.26

Received: December 16, 2022, **Accepted**: August 20, 2023, **ePublished**: August 24, 2024

Introduction

Since January 2020, SARS-CoV-2 (COVID-19) outbreak has turned to a public health emergency of international concern due to its high rates of mortality, rapid transmission (1,2), exponential growth of cases (3), diversity of symptoms (4), and dependency on empiric treatments (5,6).

Although all the age and sex groups are susceptible to COVID-19 infection, vulnerable populations such as the elderly, patients with systematic disorders and comorbidities, and pregnant women are at a higher risk of developing severe complications (7,8). Previous studies on infectious diseases such as H1N1 influenza pandemics and Zika fever suggest a higher rate of mortality in pregnant women and their developing fetuses (9,10) and further, viral pneumonia is considered as a major cause of fetal death (11). It is argued that physiologic changes during pregnancy, including alternations of immune system (12,13), adoptions of respiratory system (14), and establishment of a hypercoagulable condition (15) will all result in more susceptibility of pregnant women to get infected and consequently, experience pregnancy complications such as preeclampsia, irregular contractions (16), preterm delivery, respiratory distress, fetal distress, premature rupture of membranes (PROM) (17), disseminated intravascular coagulopathy (18), and stillbirth (19).

However, some other claim that there is poor evidence regarding the susceptibility of pregnant women to sever coronavirus infections including sever acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19 (1,4,20). The evidence supporting intrauterine transmission of COVID-19 and transmission of virus through delivery and breast feeding is insufficient (21-23) and the infection symptoms are not definitely different or worse in pregnant mothers

compared to non-pregnant women of the same age and even male patients (14,24). Moreover, the correlation between COVID-19 infection and a higher risk of fetal death is conflicting (12). The existing literature suggests that the male population are affected by COVID-19 infection as extensively as the female population are, and therefore; women and particularly pregnant women are not essentially at a higher risk (25). Thus, the possible increase in rates of pregnancy termination or fetal death in the current outbreak might also be explained by reasons other than transmission of COVID-19 virus and induced antibodies through placenta; factors such as social concerns (26), intentional abortion, and especially mental health issues (27). Prevalence of mental health problems increases during outbreaks (28,29) and it is proposed that risk of infection, social isolation, domestic conflicts, and economic insecurity play a significant role in developing pregnancy-related anxiety during COVID-19 pandemics (30).

Hypercoagulable state may have an important role in both pregnancy and COVID-19 infection. D-Dimer, the smallest fibrin fragment which may increase in blood after clot degradation may increase in normal pregnancies according to gestation age (31). In addition, studies have shown that infection with corona virus increases the possibility of clot formation (32). Considering the current controversy in literature, whether COVID-19 infection can change the incidence of fetal death in pregnant women, the present study aims to describe the fetal mortality rate (FMR) in five major hospitals in Kerman, Iran in a period of three months in outbreak, matched to the same period in non-COVID period in the prior year. Also, coagulopathy and anxiety were investigated as possible risk factors for fetal death.

Methods

Study design and setting

The present study is retrospective research, carried out in five major hospitals in Kerman, Iran. The data related to study variables was extracted from the hospital records in two separate and matched intervals: March 20, 2020, to June 20, 2020 (COVID-19) and March 21, 2019, to June 21, 2019 (non-COVID-19). All inpatients aged 17 to 51 were considered to enter the study through convenience sampling.

Assessment of fetal mortality rate

The FMR is considered one of the best indicators of the health care quality provided during pregnancy and childbirth. FMR is calculated using the number of total fetal deaths in the numerator and the number of total births (live and dead births) in the denominator but by varying the criteria for gestational age and weight to define fetal death. To describe the effects of COVID-19 pandemic on FMR, the delivery status of all pregnant 17 to 51 years old women attributed to five major hospitals of Kerman city, including the total numbers of abortion, preterm delivery, and normal delivery were extracted by the study authors or hospital staff. Any history of fetal death or successful pregnancy was noted.

Assessment of coagulopathy

The patients were classified into younger (85 cases of 222) and older (137 cases of 222) than 30 years old subgroups. The evidence suggests that both pregnancy and COVID-19 infection induce hypercoagulation by triggering coagulation and fibrinolytic cascade, mostly featured with elevation of D-dimer levels and prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) (33, 34). Therefore, the values of D-dimer and PT in pregnant women were obtained from the hospital records regardless of employed laboratory method or equipment.

Assessment of anxiety

Maternal general anxiety in COVID-19 outbreak was evaluated using PROMIS-Anxiety Short Form. The participants were contacted and the Persian version of PROMIS-Anxiety Short Form was used to interview the patients by a psychologist. The questionnaire consisted of 8 Items each scoring 1 to 5 and an overall score of 8 to 40, an overall T-score ranging 60-69.9 is indicative of moderately elevated anxiety symptoms and mothers with T-scores equal or greater than 70 are diagnosed with severely elevated anxiety (35). The answers to the questions were classified in either of four sub-groups: WI: women younger than 30 years with first pregnancy, WII: women younger than 30 years with previous pregnancies, WIII: women older than 30 years with first pregnancy, and WIV: women older than 30 years with previous pregnancies.

Assessment of maternal and fetal death age

The data related to the maternal and fetal death age were collected from available files of both groups. Mean and standard deviation were calculated and *t* test were used to compare the data. The correlation between maternal age and fetal death age was also studied.

Statistical analysis

The difference in frequency of fetal death incidence between COVID-19 and non-COVID-19 span was analyzed using chi-square test. For the purpose of risk estimation, the odds ratio (OR) was calculated with a confidence interval of 95%; significance level was set to be 0.05. The analysis was carried out using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

Results

Fetal mortality rate

A comparison of FMR during COVID-19 and non-

COVID-19 span is shown in Table 1. During the COVID-19 period, the frequency of fetal death increased in comparison to the parity (10.86% vs 7.97%). Also, the risk of fetal death was 40% higher in COVID-19 period (OR = 1.40, 95% CI: 1.14 – 1.72, $P = 0.0012$).

Laboratory findings

PT and aPTT tests were analyzed in 26% of younger pregnant individuals (22 cases) and 38% of older ones (52 cases). The results indicated that 59% of the first group and 79% of second group had mildly prolonged PT and aPTT time. Unfortunately, D-dimer test was done for only 7.2% of all pregnant individuals (16 of 222 cases), and its level in 69% of these mothers (11 cases) was higher than the normal level.

Anxiety

Maternal general anxiety was assessed by PROMIS form. In WI group, 64% of the participants filled the questionnaire and approximately 4% of them had symptoms of mild anxiety. Participation rates in WII, WIII, and WIV groups were 46.5%, 76.5%, and 66.5%, respectively. Of WII participants, 10% showed moderate and 5% showed severe anxiety symptoms. 23% of women in WIII group had severe anxiety symptoms, and in WIV group, about 11% had moderate anxiety and 2.5% were severely anxious.

Comparison of anxiety in women based on the number of pregnancies

Table 2 shows the average anxiety in women based on the number of pregnancies.

Table 3 shows the results of the t-test for comparing anxiety in women based on the number of pregnancies.

The significant level of Levene's test (F = 0.44) indicating the homogeneity of anxiety variance in two groups. According to the T-test results (T = 3.59), level of anxiety in the first pregnancy is significantly higher than other pregnancies.

Maternal and Fetal death age

Table 4 shows the mean and SD of maternal and fetal death age in two groups.

Based on the data in the table above; The mean and SD of fetal death age was (9.96 ± 3.44 months) in Covid infected group while it was (9.79 ± 3.64 months) in non-infected group. T-test was used to compare the age of fetal death in the two groups. Table 5 shows the results of the independent t-test in this area.

According to the results of Levene's test for evaluating the homogeneity of variable variance in the studied groups, considering that the value (F = 0.34) is at a level higher than ($P < 0.05$), it can be said that the variances are homogeneous. The results of the t-test with statistical value (T = 0.48) and ($df = 401$) indicate that there is no significant difference in the age of fetal death during and before the Covid period.

Table 6 shows the correlation between maternal and fetal death ages.

The results revealed that this correlation was significant (R = 0.58) at the level of ($P < 0.01$). In other words, increasing the maternal age increases the age of fetal death. Chi-square test was used for evaluating the status of the D-dimer trend based on age; Table 7 shows the frequency of D-dimer status at age intervals.

Table 8 shows the observed and the expected frequency in the chi-square test.

Table 9 shows the final results of the chi-square test to examine the trend of changes in the D-dimer index based on aging. According to the results, the obtained statistical value (8.22) with (df = 4) is significant at the

Table 1. Frequency of fetal death during COVID-19 and non-COVID-19 spans

Time span	Fetal death		OR (95% CI)	*P* value
	Yes, N (%)	No, N (%)		
COVID-19	222 (10.86)	1823 (7.97)	1.40 (1.14–1.72)	0.0012*
Non-COVID-19	180 (89.14)	2078 (92.03)		

* Significant at $P = 0.05$.

Table 2. Mean of anxiety in women by number of pregnancies

Groups	Mean	SD
First pregnancy	3.52	1.41
Second pregnancy and more	2.12	1.17

Table 3. T-test results comparing anxiety in women based on the number of pregnancies

T-test			Levene's test	
Significance level	df	T	Significance level	F
$P < 0.05$	158	3.59	0.374	0.44

Table 4. Mean and SD of maternal and abortion age in covid infected and non-infected groups

Groups	Variable	Mean	SD
COVID infected	Fetal death age (months)	9.96	3.44
Non-infected		9.79	3.64
COVID infected	Maternal age (year)	31.9	4.2
Non-infected		31.4	4.4

Table 5. Independent t-test results comparing the age of fetal death in two groups of the covid infected and non-infected periods

T-test			Levene's test	
P value	df	t	*P* value	F
0.17	401	0.48	0.55	0.34

Table 6. Correlation between maternal and fetal death age in both groups

Variable	Abortion age	*P* value
	R	
Age	0.58	<0.01

Table 7. Frequency of non-traded D-dimer condition in age interval

Age category	Frequency	Percent	Compression percentage
17-25	7	14.6	14.6
26-30	9	18.7	33.3
31-35	14	29.2	62.5
More than 35	18	37.5	100

Table 8. Observed and expected frequency in chi-square test

Age category	Observed frequency	Expected frequency
17-25	7	12
26-30	9	12
31-35	14	12
More than 35	18	12

Table 9. Final results of Chi-square test examining the trend of changes in D-dimer index based on age

Index	Value
Chi-square	8.22
df	4
P value	0.02

level of ($P < 0.05$). As a result, it can be concluded that with increasing age, the D-dimer index level increases.

Discussion

Although the first reports of COVID-19 infection dates back to more than three years ago and much endeavor has been made to identify the relevant complications and possible risk factors, there has been left significant controversies regarding the exact mechanisms of pathogenicity, appearance of symptoms, and mortality (36,37). We observed that rate of fetal death has significantly increased matched to the same period in the prior year, suggesting that COVID-19 infection, even asymptomatic, could be a risk to pregnancy outcomes. Pregnancy, by nature, alters the biologic functions to preserve the allogenic fetus, assist in fetus development, and also protect mother and fetus against pathogenic agents (16). Regarding the respiratory system, functional residual volume reduces, diaphragm elevates, and respiratory mucosa becomes edematous. Limitation of lungs to expand, and upper respiratory tract contracts due to elevated levels of estrogen and progesterone; which all put the pregnant mother at a higher risk of getting infected by air-borne pathogens (14). Furthermore, the mother immunity undergoes three different stages: proinflammatory phase in the first trimester resulting in placenta formation and fetus implementation, anti-inflammatory phase in the second trimester to help the fetus grow, and another proinflammatory phase in the third trimester for advancement of pregnancy and delivery (38). These adoptions lead to a state called "immune clock" mainly featured by increased susceptibility of innate immune cells (such as NK cells and monocytes) and suppression of T and B cells. However, lymphopenia is known to be correlated with severity of symptoms and need to critical care in COVID-19 cases (39,40). On the other hand, the literature suggest that COVID-19 infection is likely to trigger a cytokine-storm with mediation of antibody dependent enhancement (ADE), manifesting severe inflammatory responses, particularly in the first and the third trimester, that in turn will induce pregnancy adverse outcomes and fetus neural dysfunctions (41-44). Hemostasis is another biologic procedure with major changes during pregnancy that appears with a hypercoagulative state that includes an increase of fibrinogen and D-dimers by 50% which, the latter is an indicator of poor prognosis in COVID-19 patients (45,46). Some other also suggest that mortality rates increase with prolongation of PT and aPTT, thrombocytopenia, and fibrinogen decrease as a result of elevated fibrin degeneration in COVID-19 inpatients (47-49). Our findings indicates that PT and aPTT has mildly increased in 59% of WI and WII, and by 79% in WIII and WIIII participants. Our investigation is the study to question the coagulopathy as a risk factor of fetal death in COVID-19 setting. There are case report studies confirming COVID-19 coagulopathies in pregnancy: progressive thrombocytopenia, prolonged aPTT, fibrinogen reduction, and elevation of D-dimer in two cases (50), pulmonary embolism (51), and thrombosis in ovarian vein (52).

While, we could not gain the laboratory data of all women but our findings have shown coagulation problems may be in relation to fetal death in pregnancy. Furthermore, this study identify increase age is a risk factor for coagulopathy and fetal death in pregnancy. In addition to, our findings showed that anxiety have been known as a risk factor for fetal death. Since the level of anxiety in first pregnancy women was higher than women with previous pregnancy; So, obtaining fetal death reduction depend on more attention to first pregnancy women in pandemic period.

The level of anxiety in first pregnancy women was higher than no first pregnancy women. So, first pregnancy women need more attention to fetal death reduction. A large body literature propose that catecholamines mediate the severity of anxiety symptoms by modulating limbic structures and amygdala, (53). Excessive levels of catecholamines in pregnant women is associated with arterial hypertension and later with gestational hypertension, preeclampsia, and eclampsia which all may lead to fetal death (54, 55). Also, pregnancy-related anxiety is associated with higher risk of pre-term birth and low birth weight (56).

We observed a significantly higher rate of fetal death in COVID-19 setting and we suggest coagulopathy and anxiety as a main risk factor of such adverse effect. Data regarding vertical transmission of virus through placenta is lacking, hence, presence of the virus in amniotic fluid,

cord blood, and breast milk in COVID-19-possitive mothers is not evident yet. However, a case report study indicates ischemic-hemorrhagic lesions in a COVID-19 patient placenta in her second trimester, suggesting that fetal loss is caused by a local inflammation and expression of angiotensin-converting enzyme 2 receptor (ACE2) in placental tissue and essentially, ACE-2 receptor expression is the reason why pregnant woman are at a higher risk of obstetrical complications following SARS-CoV-2 infection (57,58). ACE-2 is the mediator of binding coronaviruses to the host cells and although this enzyme has shown to have beneficial effects in acute injuries of respiratory system, over expression of this enzyme in response to oestrogens elevation can lead to more susceptibility to SARS-CoV-2 infection and pregnancy adverse outcomes (59). In another case report of second trimester stillbirth, accumulation of neutrophiles and monocytes in the sub-chorial space, intervillous thrombosis, and inflammation of umbilical connective tissue has been observed as histopathologic findings of placenta (60).

Conclusion

Concerning the limitations of this study, it should be mentioned that if possible congenital defects had been primarily monitored in aborted fetuses it could be informative; however, unfortunately, we were not able to check infections in aborted fetuses. Overall, the data obtained from the present investigation showed during the COVID-19 pandemic, pregnant women are at significantly higher risk of fetal death, compared to the healthy pregnant population. Vascular coagulation without other symptoms of disease and elevated anxiety and disruption to receiving prenatal care grow unsuccessful pregnancy in pandemic period.

So, an appropriate strategy should be taken to check out the rate of the infection of the SARS-CoV-2 in asymptomatic pregnant individuals at the perinatal period, and more precise care and social supports should be considered to the pregnant patients.

Acknowledgements

The authors would like to thank the Department of Anatomical Sciences, Afzalipour School of Medicine, Kerman University of Medical Sciences for their support.

Authors' Contribution

Conceptualization: Mona Saheli, Masoumeh Baghalishahi.
Data curation: Mona Saheli, Masoumeh Baghalishahi.
Formal analysis: Hossein Bonakchi.
Investigation: Mona Saheli, Masoumeh Baghalishahi, Hossein Bonakchi.
Methodology: Mona Saheli, Masoumeh Baghalishahi, Shahrzad Sadat Eftekharvaghefi, Vida Mirzaie.
Project administration: Mona Saheli.
Resources: Mona Saheli, Masoumeh Baghalishahi.
Software: Vida Mirzaie, Hossein Bonakchi.
Supervision: Mona Saheli, Masoumeh Baghalishahi.
Validation: Mona Saheli, Masoumeh Baghalishahi, Shahriar Dabiri.
Visualization: Mona Saheli, Masoumeh Baghalishahi.
Writing–original draft: Mona Saheli, Masoumeh Baghalishahi.

Competing Interests

The authors declare that they have no competing interests.

Ethical Approval

This study was approved by the Ethics Committee of Kerman University of Medical Sciences (code: IR.KMU.REC.1398.143).

Funding

None.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. doi: 10.1016/s0140-6736(20)30183-5.
2. Abuelgasim E, Saw LJ, Shirke M, Zeinah M, Harky A. COVID-19: Unique public health issues facing Black, Asian and minority ethnic communities. Curr Probl Cardiol. 2020;45(8):100621. doi: 10.1016/j.cpcardiol.2020.100621.
3. Zhao S, Lin Q, Ran J, Musa SS, Yang G, Wang W, et al. Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: a data-driven analysis in the early phase of the outbreak. Int J Infect Dis. 2020;92:214-7. doi: 10.1016/j.ijid.2020.01.050.
4. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13. doi: 10.1016/s0140-6736(20)30211-7.
5. Centers for Disease Control and Prevention (CDC). Interim Infection Prevention and Control Recommendations for Patients with Confirmed 2019 Novel Coronavirus (2019-nCoV) or Patients Under Investigation for 2019-nCoV in Healthcare Settings. 2020. Available from: https://www.cdc.gov/coronavirus/2019-nCoV/hcp/infection-control.html. Accessed January 3, 2022.
6. Centers for Disease Control and Prevention (CDC). Interim Guidance for Implementing Home Care of People Not Requiring Hospitalization for 2019 Novel Coronavirus (2019-nCoV). 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-homecare.html?CDC_AA_refValhttps%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fguidance-home-care.html. Accessed January 3, 2022.
7. Lipsitch M, Swerdlow DL, Finelli L. Defining the epidemiology of COVID-19 - studies needed. N Engl J Med. 2020;382(13):1194-6. doi: 10.1056/NEJMp2002125.
8. Jordan RE, Adab P, Cheng KK. COVID-19: risk factors for severe disease and death. BMJ. 2020;368:m1198. doi: 10.1136/bmj.m1198.
9. Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA. 2010;303(15):1517-25. doi: 10.1001/jama.2010.479.
10. Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika virus and birth defects--reviewing the evidence for causality. N Engl J Med. 2016;374(20):1981-7. doi: 10.1056/NEJMsr1604338.
11. Dashraath P, Wong JLJ, Lim MX, Lim LM, Li S, Biswas A, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol. 2020;222(6):521-31. doi: 10.1016/j.ajog.2020.03.021.
12. Ortiz EI, Herrera E, De La Torre A. Coronavirus (COVID 19)

infection in pregnancy. Colomb Med (Cali). 2020;51(2):e4271. doi: 10.25100/cm.v51i2.4271.
13. Li Y, Zhao R, Zheng S, Chen X, Wang J, Sheng X, et al. Lack of vertical transmission of severe acute respiratory syndrome coronavirus 2, China. Emerg Infect Dis. 2020;26(6):1335-6. doi: 10.3201/eid2606.200287.
14. Liu W, Wang Q, Zhang Q, Chen L, Chen J, Zhang B, et al. Coronavirus disease 2019 (COVID-19) during pregnancy: a case series. Preprints. 2020. Available from: https://www.preprints.org/manuscript/202002.0373/v1.
15. Kadir RA, Kobayashi T, Iba T, Erez O, Thachil J, Kazi S, et al. COVID-19 coagulopathy in pregnancy: critical review, preliminary recommendations, and ISTH registry-communication from the ISTH SSC for Women's Health. J Thromb Haemost. 2020;18(11):3086-98. doi: 10.1111/jth.15072.
16. Liu H, Wang LL, Zhao SJ, Kwak-Kim J, Mor G, Liao AH. Why are pregnant women susceptible to COVID-19? An immunological viewpoint. J Reprod Immunol. 2020;139:103122. doi: 10.1016/j.jri.2020.103122.
17. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr. 2020;9(1):51-60. doi: 10.21037/tp.2020.02.06.
18. Liu D, Li L, Wu X, Zheng D, Wang J, Liang B, et al. Pregnancy and Perinatal Outcomes of Women with COVID-19 Pneumonia: A Preliminary Analysis. 2020. Available from: https://ssrn.com/abstract=3548758.
19. Cosma S, Carosso AR, Cusato J, Borella F, Carosso M, Bovetti M, et al. Coronavirus disease 2019 and first-trimester spontaneous abortion: a case-control study of 225 pregnant patients. Am J Obstet Gynecol. 2021;224(4):391.e1-391.e7. doi: 10.1016/j.ajog.2020.10.005.
20. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9. doi: 10.1001/jama.2020.1585.
21. 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.
22. Yan J, Guo J, Fan C, Juan J, Yu X, Li J, et al. Coronavirus disease 2019 in pregnant women: a report based on 116 cases. Am J Obstet Gynecol. 2020;223(1):111.e1-111.e14. doi: 10.1016/j.ajog.2020.04.014.
23. Akhtar H, Patel C, Abuelgasim E, Harky A. COVID-19 (SARS-CoV-2) infection in pregnancy: a systematic review. Gynecol Obstet Invest. 2020;85(4):295-306. doi: 10.1159/000509290.
24. 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.
25. Bateson DJ, Lohr PA, Norman WV, Moreau C, Gemzell-Danielsson K, Blumenthal PD, et al. The impact of COVID-19 on contraception and abortion care policy and practice: experiences from selected countries. BMJ Sex Reprod Health. 2020;46(4):241-3. doi: 10.1136/bmjsrh-2020-200709.
26. 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. doi: 10.1016/j.ajog.2020.02.017.
27. Mohammed SH, Ali RM. Assessment of psychological risk factors for spontaneous abortion at maternity wards in Baghdad city hospitals. Indian J Forensic Med Toxicol. 2020;14(4):2425-9.
28. Tomfohr-Madsen LM, Racine N, Giesbrecht GF, Lebel C, Madigan S. Depression and anxiety in pregnancy during COVID-19: a rapid review and meta-analysis. Psychiatry Res. 2021;300:113912. doi: 10.1016/j.psychres.2021.113912.
29. Lebel C, MacKinnon A, Bagshawe M, Tomfohr-Madsen L, Giesbrecht G. Elevated depression and anxiety symptoms among pregnant individuals during the COVID-19 pandemic. J Affect Disord. 2020;277:5-13. doi: 10.1016/j.jad.2020.07.126.
30. Moyer CA, Compton SD, Kaselitz E, Muzik M. Pregnancy-related anxiety during COVID-19: a nationwide survey of 2740 pregnant women. Arch Womens Ment Health. 2020;23(6):757-65. doi: 10.1007/s00737-020-01073-5.
31. Baboolall U, Zha Y, Gong X, Deng DR, Qiao F, Liu H. Variations of plasma D-dimer level at various points of normal pregnancy and its trends in complicated pregnancies: a retrospective observational cohort study. Medicine (Baltimore). 2019;98(23):e15903. doi: 10.1097/md.0000000000015903.
32. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J Clin Virol. 2020;127:104362. doi: 10.1016/j.jcv.2020.104362.
33. Iba T, Levy JH, Levi M, Thachil J. Coagulopathy in COVID-19. J Thromb Haemost. 2020;18(9):2103-9. doi: 10.1111/jth.14975.
34. Mucha SR, Dugar S, McCrae K, Joseph D, Bartholomew J, Sacha GL, et al. Coagulopathy in COVID-19: manifestations and management. Cleve Clin J Med. 2020;87(8):461-8. doi: 10.3949/ccjm.87a.ccc024.
35. Lebel C, MacKinnon A, Bagshawe M, Tomfohr-Madsen L, Giesbrecht G. Corrigendum to elevated depression and anxiety symptoms among pregnant individuals during the COVID-19 pandemic journal of affective disorders 277 (2020) 5-13. J Affect Disord. 2021;279:377-9. doi: 10.1016/j.jad.2020.10.012.
36. Mokhtari T, Hassani F, Ghaffari N, Ebrahimi B, Yarahmadi A, Hassanzadeh G. COVID-19 and multiorgan failure: a narrative review on potential mechanisms. J Mol Histol. 2020;51(6):613-28. doi: 10.1007/s10735-020-09915-3.
37. Renu K, Prasanna PL, Valsala Gopalakrishnan A. Coronaviruses pathogenesis, comorbidities and multi-organ damage - a review. Life Sci. 2020;255:117839. doi: 10.1016/j.lfs.2020.117839.
38. Mor G, Aldo P, Alvero AB. The unique immunological and microbial aspects of pregnancy. Nat Rev Immunol. 2017;17(8):469-82. doi: 10.1038/nri.2017.64.
39. Aghaeepour N, Ganio EA, McIlwain D, Tsai AS, Tingle M, Van Gassen S, et al. An immune clock of human pregnancy. Sci Immunol. 2017;2(15):eaan2946. doi: 10.1126/sciimmunol.aan2946.
40. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang YQ, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther. 2020;5(1):33. doi: 10.1038/s41392-020-0148-4.
41. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-81. doi: 10.1016/s2213-2600(20)30079-5.
42. Tetro JA. Is COVID-19 receiving ADE from other coronaviruses? Microbes Infect. 2020;22(2):72-3. doi: 10.1016/j.micinf.2020.02.006.
43. Yu D, Rao S, Tsai LM, Lee SK, He Y, Sutcliffe EL, et al. The transcriptional repressor Bcl-6 directs T follicular helper cell lineage commitment. Immunity. 2009;31(3):457-68. doi:

10.1016/j.immuni.2009.07.002.
44. Fried M, Kurtis JD, Swihart B, Pond-Tor S, Barry A, Sidibe Y, et al. Systemic inflammatory response to malaria during pregnancy is associated with pregnancy loss and preterm delivery. Clin Infect Dis. 2017;65(10):1729-35. doi: 10.1093/cid/cix623.
45. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. Obstet Gynecol. 2009;114(6):1326-31. doi: 10.1097/AOG.0b013e3181c2bde8.
46. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020;18(6):1421-4. doi: 10.1111/jth.14830.
47. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-7. doi: 10.1111/jth.14768.
48. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18(5):1023-6. doi: 10.1111/jth.14810.
49. Hunt B, Retter A, McClintock C. Practical Guidance for the Prevention of Thrombosis and Management of Coagulopathy and Disseminated Intravascular Coagulation of Patients Infected with COVID-19. Available from: https://thrombosisuk.org/downloads/T&H%20and%20COVID.pdf. Accessed April 28, 2020.
50. Vlachodimitropoulou Koumoutsea E, Vivanti AJ, Shehata N, Benachi A, Le Gouez A, Desconclois C, et al. COVID-19 and acute coagulopathy in pregnancy. J Thromb Haemost. 2020;18(7):1648-52. doi: 10.1111/jth.14856.
51. Martinelli I, Ferrazzi E, Ciavarella A, Erra R, Iurlaro E, Ossola M, et al. Pulmonary embolism in a young pregnant woman with COVID-19. Thromb Res. 2020;191:36-7. doi: 10.1016/j.thromres.2020.04.022.
52. Mohammadi S, Abouzaripour M, Hesam Shariati N, Hesam Shariati MB. Ovarian vein thrombosis after coronavirus disease (COVID-19) infection in a pregnant woman: case report. J Thromb Thrombolysis. 2020;50(3):604-7. doi: 10.1007/s11239-020-02177-6.
53. Ferrazzo S, Gunduz-Cinar O, Stefanova N, Pollack GA, Holmes A, Schmuckermair C, et al. Increased anxiety-like behavior following circuit-specific catecholamine denervation in mice. Neurobiol Dis. 2019;125:55-66. doi: 10.1016/j.nbd.2019.01.009.
54. Lenders JW. Pheochromocytoma and pregnancy: a deceptive connection. Eur J Endocrinol. 2012;166(2):143-50. doi: 10.1530/eje-11-0528.
55. Misasi G, Pancetti F, Giannini A, Simoncini T, Mannella P. Pheochromocytoma diagnosed during pregnancy: a case report. Gynecol Endocrinol. 2020;36(7):650-3. doi: 10.1080/09513590.2020.1754392.
56. Dunkel Schetter C. Psychological science on pregnancy: stress processes, biopsychosocial models, and emerging research issues. Annu Rev Psychol. 2011;62:531-58. doi: 10.1146/annurev.psych.031809.130727.
57. Li M, Chen L, Zhang J, Xiong C, Li X. The SARS-CoV-2 receptor ACE2 expression of maternal-fetal interface and fetal organs by single-cell transcriptome study. PLoS One. 2020;15(4):e0230295. doi: 10.1371/journal.pone.0230295.
58. Narang K, Enninga EAL, Gunaratne M, Ibirogba ER, Trad ATA, Elrefaei A, et al. SARS-CoV-2 infection and COVID-19 during pregnancy: a multidisciplinary review. Mayo Clin Proc. 2020;95(8):1750-65. doi: 10.1016/j.mayocp.2020.05.011.
59. Todros T, Masturzo B, De Francia S. COVID-19 infection: ACE2, pregnancy and preeclampsia. Eur J Obstet Gynecol Reprod Biol. 2020;253:330. doi: 10.1016/j.ejogrb.2020.08.007.
60. Baud D, Greub G, Favre G, Gengler C, Jaton K, Dubruc E, et al. Second-trimester miscarriage in a pregnant woman with SARS-CoV-2 infection. JAMA. 2020;323(21):2198-200. doi: 10.1001/jama.2020.7233.