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Hematological Changes and Pregnancy Outcome in COVID-19 Pregnant Patients: A Case–Control Study

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Abstract

BACKGROUND: Viral infections during pregnancy are associated with adverse maternal as well as fetal outcomes such as higher rates of miscarriage, perinatal mortality, restriction of fetal growth, and preterm delivery.

AIM: The aim of the study was to explore maternal outcomes and hematological alterations in a sample of Iraqi pregnant women.

PATIENTS AND METHODS: The present cross-sectional study was carried out in the Obstetric Department in Al *Imamain* Al-Kadhimain *Medical City, Baghdad, Iraq, including a total of 55 full-term pregnant women who were grouped into 25 women with SARS-CoV-2 and 30 control pregnant women, starting from* January 2021 to December 2021. Pregnant women admitted to hospital for the purpose of delivery were routinely examined and assessed, and then, nasopharyngeal swab was obtained for the purpose of PCR testing for SARS-CoV-2. Then, 3 ml of venous blood was obtained from the antecubital vein following sterilization and the blood was transferred to the central hospital laboratory to do complete blood count within 24 h using the automated hematological analyzer that the results were then transferred into an Office Excel sheet for the future statistical analysis.

RESULTS: Among the hematological variables that were analyzed, the mean WBC count and mean lymphocyte count were lower in COVID-19 group to compared category and the variation was significant ($p < 0.001$); however, there was no significant difference in mean neutrophil count. There has been no significant variation in mean hemoglobin, mean RBC count, mean PCV, mean MCV, mean MCH, and mean RDW between control group and COVID-19 group ($p > 0.05$). Moreover, there was no significant difference in mean platelet count, mean platelet distribution width, and mean platelet volume ($p > 0.05$).

CONCLUSION: COVID-19 at time of pregnancy is accompanied by significantly lower leukocyte and lymphocyte count in comparison with non-infected pregnant women in addition to higher rate of cesarean section due to fetal distress with no significant increase in fetal or maternal mortality rates.

Introduction

A cluster of four instances of pneumonia of unclear cause was reported to the “World Health Organization” in December 2019 in Wuhan, China [1]. Since then, “coronavirus disease 2019 (COVID-19),” which is occurred due to “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)” has rapidly extent over the world. The WHO acknowledged the outbreak a pandemic on March 12, 2020 [2]. To focus resources on COVID-19 treatment, many governments restricted free will of movement and limited non-emergency health maintenance [3].

When COVID-19 pandemic became the most common health issue worldwide, pregnant women were recognized as one of the high-risk groups taking into consideration the possibility of increasing incidence of severe clinical presentation and development of adverse outcomes [1], [4]. “The International Federation of Gynecology and Obstetrics” suggested that extensive regular antenatal care be suspended and replaced with telephone or video conversation whenever applicable to limit transmission hazards for both health-care providers and pregnant women [5]. SARS-CoV-2 is a solitary RNA stranded capsulated virus. COVID-19’s immunological reaction, like that of other viruses, is dependent on a functioning immune structure. Infection by COVID-19 can cause either severe status, with significant fatality rates or moderate illness, in which the virus eliminated by immunity system [1].

On this spectrum, the status of pregnant women is unknown. During pregnancy, the immune system adjusts to let for the development of a semi allogenic fetus, leading to changed immunological reaction to infections [6]. The molecular mechanisms and pathophysiology of COVID-19 must be understood in the setting of the modified mother immune reaction to comprehend the COVID-19 phenotype during pregnancy [1]. Added to the systemic immunological alterations that can affect lung function during pregnancy, anatomical alterations in the respiratory system are also evident. Changes in respiratory function are caused by physiological changes in the chest configuration and diaphragm elevation caused by splinting of the diaphragm by the gravid uterus. Although tidal volume

increases by 30–40%, the decrease in the volume of chest causes a reduction in effective residual capacity, residual volumes, and end-expiratory volumes, starting early in gestation.

Pregnant ladies are more prone to severe infections of respiratory tract due to an inability to discharge secretions and a decrease in total lung capacity [7], [8]. Moreover, COVID-19 is related with increasing rates of thromboembolic events and this will add to the already existing hypercoagulable status of pregnancy [9], [10], [11]. Viral infections during pregnancy are associated with adverse maternal as well as fetal outcomes such as higher rates of perinatal death, preterm delivery, restriction of fetal growth, and miscarriage [1]. In view of above mentioned data and the rarity of Iraqi literatures dealing with adverse consequences of COVID-19 in association with pregnancy, the planning and conduction of the present study were justified aiming at exploring maternal outcomes and hematological alterations in a sample of Iraqi pregnant women. Indeed, our clinical observation showed that pregnant women with COVID-19 suffered a number of obstetric as well as medical conditions and research work with this regard is still in its beginning so we want to explore the effect of having COVID-19 on obstetrical outcomes in additions, a number of the previous studies have shown some adverse obstetric outcomes in association with COVID-19 [1], [12], [13], [14], [15], [16]. One previous review has shown increased need for assisted ventilation and admission to intensive care unit [1].

Patients and Methods

Study design

The present cross-sectional study was carried out in the Obstetric Department in Al *Imamain* Al-Kadhimain *Medical City, Baghdad, Iraq. The study included a total of 55 full-term pregnant women who were grouped into 25 women with COVID-19 according to* the *clinical manifestations and PCR results and 30 non-infected pregnant women with no COVID-19.* The study stared on January 2021 and extended to December 2021.

Methods

Evaluation of clinical features of patients' groups was done. Obstetric history, age, gestational age, fetal, and maternal outcomes were carried out to both groups. Fetal outcome was assessed through APGAR score and rate of neonatal admission to intensive care unit. Maternal outcome was assessed through rate of admission to intensive care unit and needs to oxygen therapy. In addition, rate of cesarean section was assessed in both groups.

Pregnant women admitted to hospital for the purpose of delivery were routinely examined and assessed, and then, nasopharyngeal swab was obtained for the purpose of PCR testing for SARS-CoV-2. Then, 3 ml of venous blood was obtained from the antecubital vein following sterilization and the blood was transferred to the central hospital laboratory to do complete blood count within 24 h using the automated hematological analyzer that the results were then transferred into an Office Excel sheet for the future statistical analysis.

Ethical considerations

The study was approved by the Ethical Approval Committee of college of medicine/Al-Nahrain University/ Baghdad and formal agreement was issued by the directorate of health (under the number 202202142) in February 2021. Written consent was obtained from each participant. Full illustration of the study aims and procedures were carried out to all participants.

Statistical analysis

Microsoft Office Excel 2010 and package for the social sciences version 23 were used to analysis of data included in the present study. Presentation of categorical variables was done using number and percentage. Quantitative variables were presented as mean and standard deviation or as median and inter-quartile range based on normality distribution. The association between qualitative variables (mode of delivery, obstetric events, and admission to intensive care unit) was based on Chi-square test. Yates correction or Fischer exact test was used instead, when >20% of cells have expected counts of <5.

Student t-test or Mann–Whitney U test was used to the study difference in mean or median of quantitative variables, respectively, between any two groups based on normality distribution. When $p < 0.05$, it was considered significant.

Results

The general characteristics of pregnant women enrolled in the present study categorized into control group and COVID-19 group are shown in Table 1. Mean age showed no significant variation between COVID-19 group and control group, 25.44 ± 4.54 years versus 27.10 ± 4.92 years, respectively ($p = 0.202$). Mean gestational age also showed no significant variation

between COVID-19 group and control category, 36.56 ± 1.58 weeks versus 36.87 ± 1.01 weeks, respectively (p = 0.388). There was also no significant difference in mean BMI between COVID-19 group and control group (p = 0.199).

Table 1: General characteristics of pregnant women enrolled in the present study categorized into control group and COVID-19 group

Characteristic	COVID-19 n = 25	Control group n = 30	p
Age (years)			
Mean ± SD	25.44 ± 4.54	27.10 ± 4.92	0.202 I
Range	18–34	19–36	†
Gestational age (weeks)			
Mean ± SD	36.56 ± 1.58	36.87 ± 1.01	0.388 I
Range	32–40	35–39	†
BMI (kg/m^2)			
Mean ± SD	28.56 ± 1.03	28.91 ± 0.94	0.199 I
Range	26.9–31.2	27.6–30.9	†
Parity			
Median (IQR)	2 (2)	3 (2)	0.097 M
Range	1–5	1–7	NS

n: Number of cases, SD: Standard deviation, IQR: Inter-quartile range, I: Independent samples t-test, M: Mann–Whitney U test, †: Not significant at p > 0.05

In addition, there has been no significant difference in median parity between COVID-19 and control group, 2 (2) versus 3 (2), respectively (p = 0.097). The clinical manifestations of pregnant ladies with COVID-19 are demonstrated in Table 2.

Table 2: Clinical manifestations of pregnant ladies having COVID-19

Clinical manifestations	N	%
Asymptomatic	5	20.0
Cough	9	36.0
Fever	12	48.0
GIT symptoms	2	8.0

n: Number of cases

Asymptomatic cases accounted for 5 cases (20.0%), while symptomatic cases accounted for 20 cases (80%). Fever was the most common symptom which was reported in 12 cases (48.0%) and it was followed by cough which was seen in 9 cases (36.0%). Gastrointestinal symptoms in the form of nausea, vomiting, and diarrhea were seen in 2 cases (8.0%). Obstetric events contrasted between control group and COVID-19 group are shown in Table 3.

Table 3: Obstetric events contrasted between control group and COVID-19 group

Obstetric event	COVID-19 n = 25	Control group n = 30	p
Leaking liquor	1 (4.0%)	0 (0.0%)	0.455 F †
Pregnancy-induced hypertension	2 (8.0%)	0 (0.0%)	0.202 F †
Antepartum hemorrhage	2 (8.0%)	0 (0.0%)	0.202 F †
Gestational diabetes mellitus	2 (8.0%)	0 (0.0%)	0.202 F †

n: Number of cases, F: Fischer exact test, †: Not significant at *P*>0.05

Leaking liquor was seen in a single case of COVID-19 women. Pregnancy-induced hypertension, antepartum hemorrhage, and diabetes mellitus were seen in two cases of COVID-19 women for each event; however, the variation in these events between COVID-19 group and control group was not significant (p > 0.05). The comparison of mode of delivery between COVID-19 group and control group is shown in Table 4. The rate of cesarean section was higher in COVID-19 group in comparison with control group, 19 (76.0%) versus 13 (43.3%), respectively, and the difference was significant (p = 0.014). The risk of cesarean section in COVID-19 is, therefore, 4.14 times that seen in pregnant women without COVID-19 with a confidence interval of 1.29–13.31.

Maternal and fetal outcome contrasted between COVID-19 and control group is shown in Table 5. There has been no significant variation in mean APGAR score at 1 min and at 5 min between COVID-19 and control group (p > 0.05). There was also no significant difference in rate of admission to neonatal intensive care unit (p = 0.502). Nevertheless, admission to maternal intensive care unit and need for O_2 therapy was limited to COVID-19 group as it was seen in three cases accounting for 12.0%, but from statistical perspective, the difference was not significant (p = 0.088).

Table 4: Comparison of mode of delivery between COVID-19 group and control group

Mode of delivery	COVID-19 n = 25	Control group n = 30	P	OR (95% CI)
Cesarean section	19 (76.0%)	13 (43.3%)	0.014 C ¥	4.14 (1.29–13.31)
Vaginal delivery	6 (24.0%)	17 (56.7%)		

C: Chi-square test, n: Number of cases, ¥: Significant at p ≤ 0.05, OR: Odds ratio, CI: Confidence interval

Hematological characteristics contrasted between COVID-19 and control group are demonstrated in Table 6. Mean WBC count and mean lymphocyte count were lower in COVID-19 group to compared category and the variation was significant (p < 0.001); however, there was no significant difference in mean neutrophil count. There has been no significant variation in mean hemoglobin, mean RBC count, mean PCV, mean MCV, mean MCH, and mean RDW between control group and COVID-19 group (p > 0.05). Moreover, there was no significant difference in mean platelet count, mean platelet distribution width (PDW), and mean platelet volume (MPV) (p > 0.05).

Table 5: Maternal and fetal outcome contrasted between COVID-19 and control group

Characteristic	COVID-19 n = 25	Control group n = 30	p
APGAR 1 min			
Mean ± SD	7.20 ± 0.71	7.20 ± 0.93	1.000 I
Range	6–8	4–8	†
APGAR 5 min			
Mean ± SD	7.56 ± 0.65	7.73 ± 0.58	0.302 I
Range	6–8	6–9	†
Admission to NICU			
n (%)	4 (16.0%)	2 (6.7%)	0.502 Y †
Maternal outcome (ICU)			
n (%)	3 (12.0%)	0 (0.0%)	0.088 F †

n: Number of cases, APGAR: Appearance, Pulse, Grimace, Activity, and Respiration, SD: Standard deviation, NICU: Neonatal intensive care unit, I: Independent samples t-test, Y: Yates correction test, F: Fischer exact test, †: Not significant at p>0.05, ICU: intensive care unit

Discussion

In the present study, there was no significant difference in mean age, mean gestational age, and median parity between COVID-19 group and control

Table 6: Hematological characteristics contrasted between COVID-19 and control group

Characteristic	COVID-19 n = 25	Control group n = 30	p
Hemoglobin (g/dl)			
Mean ± SD	10.48 ± 1.18	10.27 ± 1.31	0.539
Range	7.2–12.1	8.7–13.8	
WBC × 10^9/L			
Mean ± SD	6.50 ± 3.23	9.83 ± 1.44	<0.001**
Range	3.2–15.6	6.9–12.6	
Lymphocyte×10^9/L			
Mean ± SD	2.83 ± 4.06	7.05 ± 1.50	<0.001**
Range	0.5–19	2.9–11.2	
PDW %			
Mean ± SD	10.93 ± 3.47	11.82 ± 1.14	0.194
Range	0.38–15.9	10.4–14.2	
MPV (fL)			
Mean ± SD	10.12 ± 1.11	10.32 ± 1.27	0.532
Range	7.8–12.7	8.3–13.2	
Platelet × 10^9/L			
Mean ± SD	229.68 ± 109.08	209.47 ± 55.41	0.379
Range	78–513	148–343	
Neutrophil count×10^9/L			
Mean ± SD	7.38 ± 1.46	7.91 ± 0.82	0.092
Range	5.2–12.3	6.3–10.4	
PCV %			
Mean ± SD	33.80 ± 2.94	32.58 ± 3.89	0.204
Range	25.7–38.3	25.2–40.2	
RBC × 10^{12}/L			
Mean ± SD	3.97 ± 0.28	3.82 ± 0.45	0.158
Range	3.09–4.52	2.94–4.79	
MCV pg			
Mean ± SD	80.55 ± 7.40	80.62 ± 6.61	0.971
Range	64–91.4	65.7–92.6	
MCH g/dl			
Mean ± SD	27.30 ± 3.56	25.61 ± 6.77	0.265
Range	18.8–33.3	3.04–32.8	
RDW %			
Mean ± SD	15.65 ± 3.10	15.08 ± 2.67	0.463
Range	12.6–25.1	11.9–22.7	

n: Number of cases, SD: Standard deviation, IQR: Inter-quartile range, **: Significant at p ≤ 0.01

group and this is essential to avoid bias in fetal and maternal outcome that can be attributed to variation in age, gestational age, or parity. In the present study, asymptomatic cases accounted for 5 cases (20.0%) and the main symptoms were fever, cough, and gastrointestinal symptoms in that order of frequency. Indeed, it has been shown that the clinical features of COVID-19 during pregnancy are not significantly different form of general population [12].

According to Huang *et al.* [13], the most prevalent giving signs were fever and a non-productive cough, which matched our findings [14]. The obstetric events in COVID-19 group were leaking liquor, pregnancy-induced hypertension, antepartum hemorrhage, and diabetes mellitus and their rate was not significantly higher when compared to control group. In a recent meta-analysis, there was significant association between pre-eclampsia and severe COVID-19 cases [15], and in the present study, two cases of pregnancy-induced hypertension in association with COVID-19 were reported.

Despite the fact that the ways underlying the link between hypertension and COVID-19 are unknown, researchers have discovered that the virus, by binding to angiotensin-converting enzyme 2 (ACE2) receptors, can cause renin–angiotensin system malfunction and vasoconstriction [16]. Some authors have demonstrated that the infection by the virus can lead to a state of proinflammation which is followed by dysfunction of endothelium that is systemic and pregnancy-induced hypertension [17], [18]. In this study, the rate of cesarean section was higher significantly in COVID-19 group in comparison with control group and the risk of cesarean section attributed to COVID-19 is 4.14 times. In one previous meta-analysis, it has been reported that COVID-19 cases with symptoms were associated with higher rate of cesarean sections in comparison with asymptomatic case and this finding supports our observation [15]. In the previous reports about pregnancy with COVID-19, in the majority of cases, a cesarean section was performed, and some authors identified fetal distress as the basis for the decision [19], [20], [21]. In addition, in the present study, there was no significant difference in adverse maternal or fetal outcome between control group and COVID-19 group.

In one meta-analysis, severe COVID-19 has been significantly accompanied by reduced birth weight, preterm delivery, pregnancy associated diabetes, and pre-eclampsia [15] in addition, and considerable fetal and maternal morbidity and mortality was linked to COVID-19 severe cases in later meta-analysis [15]. Indeed, three incidences of maternal admission to critical care (3%) and no definite mortalities were found in a prior study of 108 gravid females with confirmed SARS-CoV-2 infection [14]. Breslin *et al.* observed two maternal ICU admissions involving mothers with increased BMI (>35) and a complex medical past, raising the question of whether COVID-19 enhances the likelihood of severe morbidity in more risk gravidities [22]. In the present study, mean WBC count and mean lymphocyte count were significantly less in COVID-19 category in comparison with control group, but, there was no significant difference in mean hemoglobin, platelet count, PDW, and MPV ($p > 0.05$). In line with our observation, leukopenia is prevalent in COVID-19 individuals and reduced lymphocyte counts the most common finding in laboratory tests [23], [24].

While the specific origin of reduced lymphocytes is unknown, it is assumed to be linked to lymphocyte production of “ACE2 receptors,” in which the virus uses to infect and destroy cells that are CD-8 and CD-4 [25]. On other possible cause of reduced lymphocytes count in the increased mastocyte synthesis by bone marrow in an attempt to promote process of phagocytosis and this is supported by the finding of Liu *et al.* [26]. COVID-19 has also been found to target hemoglobin’s beta chain, breaking the hem and causing it to acquire the ring of porphyrin, and liberating iron in a free status into blood stream [26]. If this was accurate, COVID-19 individuals would have anemia or a decreased hemoglobin level.

In contrast, it has been found that the adjusted mean variation of hemoglobin in non-severe patients with COVID-19 is much larger than in severe COVID-19 patients. The patterns of increased hemoglobin can be attributable to hemoconcentration or due to excess RBC production by bone marrow to reduce hypoxemia effect. The previous

research has linked severe COVID-19 infection to thrombocytopenia [27], [28]. In the presence of infection, the pathogenesis of thrombocytopenia is likely complex, including bone marrow response, DIC, ITP, or consumptive coagulopathy as mentioned above [29]. However, in our study, mean platelet count showed no significant variation between control group and study group and this is probably to the mild presentation of most cases.

Limitations of the study

The most important limitation was the health restriction recommendations adopted during the COVID-19 pandemic which made the communication with pregnant women and sample obtaining difficult.

Conclusion

COVID-19 at time of pregnancy is accompanied by higher rate of cesarean section due to fetal distress with no significant increase in fetal or maternal mortality rates and the main hematological changes are reduced leukocyte count and lymphocyte count.

References

1. Wastnedge EA, Reynolds RM, van Boeckel SR, Stock SJ, Denison FC, Maybin JA, *et al.* Pregnancy and COVID-19. Physiol Rev. 2021;101(1):303-18. http://doi.org/10.1152/physrev.00024.2020
   PMid:32969772
2. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed. 2020;91(1):157-60. http://doi.org/10.23750/abm.v91i1.9397
   PMid:32191675
3. Sekalala S, Forman L, Habibi R, Meier BM. Health and human rights are inextricably linked in the COVID-19 response. BMJ Glob Health. 2020;5(9):e003359. http://doi.org/10.1136/bmjgh-2020-003359
   PMid:32938607
4. 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. Am J Obstet Gynecol. 2004;191(1):292-7. http://doi.org/10.1016/j.ajog.2003.11.019
   PMid:15295381
5. Bourne T, Kyriacou C, Coomarasamy A, Al-Memar M, Leonardi M, Kirk E, *et al.* ISUOG Consensus Statement on rationalization of early-pregnancy care and provision of ultrasonography in context of SARS-CoV-2. Ultrasound Obstet Gynecol. 2020;55(6):871-8. http://doi.org/10.1002/uog.22046
   PMid:32267981
6. Silasi M, Cardenas I, Kwon JY, Racicot K, Aldo P, Mor G. Viral infections during pregnancy. Am J Reprod Immunol. 2015;73(3):199-213. http://doi.org/10.1111/aji.12355
   PMid:25582523
7. LoMauro A, Aliverti A. Respiratory physiology of pregnancy: Physiology masterclass. Breathe (Sheff). 2015;11(4):297-301. http://doi.org/10.1183/20734735.008615
   PMid:27066123
8. Goodnight WH, Soper DE. Pneumonia in pregnancy. Crit Care Med. 2005;33 Suppl 10:S390-7. http://doi.org/10.1097/01.ccm.0000182483.24836.66
   PMid:16215363
9. Ribes A, Vardon-Bounes F, Mémier V, Poette M, Au-Duong J, Garcia C, *et al.* Thromboembolic events and COVID-19. Adv Biol Regul. 2020;77:100735. http://doi.org/10.1016/j.jbior.2020.100735
   PMid:32773098
10. Fontelo P, Bastola MM, Zheng Z, Baik SH. A review of thromboembolic events in hospitalized COVID-19 patients. Thromb J. 2021;19(1):47. http://doi.org/10.1186/s12959-021-00298-3
    PMid:34187490
11. Greer IA. Hypercoagulable states and pregnancy. Curr Hematol Rep. 2002;1(1):56-62.
    PMid:12901125
12. Matar R, Alrahmani L, Monzer N, Debiane LG, Berbari E, Fares J, *et al.* Clinical presentation and outcomes of pregnant women with Coronavirus disease 2019: A systematic review and meta-analysis. Clin Infect Dis. 2021;72(3):521-33. http://doi.org/10.1093/cid/ciaa828
    PMid:32575114
13. 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. http://doi.org/10.1016/S0140-6736(20)30183-5
    PMid:31986264
14. Zaigham M, Andersson O. Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies. Acta Obstet Gynecol Scand. 2020;99(7):823-9. http://doi.org/10.1111/aogs.13867
    PMid:32259279
15. Wei SQ, Bilodeau-Bertrand M, Liu S, Auger N. The impact of COVID-19 on pregnancy outcomes: A systematic review and meta-analysis. CMAJ. 2021;193(16):E540-8. http://doi.org/10.1503/cmaj.202604
    PMid:33741725
16. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, *et al.* Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: Celebrating the 20th anniversary of the discovery of ACE2. Circ Res. 2020;126:1456-74. http://doi.org/10.1161/CIRCRESAHA.120.317015
    PMid:32264791
17. Coronado-Arroyo JC, Concepción-Zavaleta MJ, Zavaleta-Gutiérrez FE, Concepción-Urteaga LA. Is COVID-19 a risk factor for severe preeclampsia? Hospital experience in a developing country. Eur J Obstet Gynecol Reprod Biol. 2021;256:502-3. http://doi.org/10.1016/j.ejogrb.2020.09.020
    PMid:32958322
18. Todros T, Masturzo B, de Francia S. COVID-19 infection: ACE2, pregnancy and preeclampsia. Eur J Obstet Gynecol Reprod Biol. 2020;253:330. http://doi.org/10.1016/j.ejogrb.2020.08.007
    PMid:32863039
19. 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. http://doi.org/10.1016/S0140-6736(20)30360-3

PMid:32151335

20. Liu H, Liu F, Li J, Zhang T, Wang D, Lan W. Clinical and CT imaging features of the COVID-19 pneumonia: Focus on pregnant women and children. J Infect. 2020;80(5):e7-13. http://doi.org/10.1016/j.jinf.2020.03.007

PMid:32171865

21. Zhang L, Jiang Y, Wei M, Cheng BH, Zhou XC, Li J, *et al.* Analysis of the pregnancy outcomes in pregnant women with COVID-19 in Hubei province. Zhonghua Fu Chan Ke Za Zhi. 2020;55(3):166-71. http://doi.org/10.3760/cma.j.cn112141-20200218-00111

PMid:32145714

22. Breslin N, Baptiste C, Gyamfi-Bannerman C, Miller R, Martinez R, Bernstein K, *et al.* Coronavirus disease 2019 infection among asymptomatic and symptomatic pregnant women: Two weeks of confirmed presentations to an affiliated pair of New York city hospitals. Am J Obstet Gynecol MFM. 2020;2(2):100118. http://doi.org/10.1016/j.ajogmf.2020.100118

PMid:32292903

23. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, *et al.* Clinical characteristics of Coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20. http://doi.org/10.1056/NEJMoa2002032

PMid:32109013

24. 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. http://doi.org/10.1001/jama.2020.1585

PMid:32031570

25. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, *et al.* Clinical and immunological features of severe and moderate Coronavirus disease 2019. J Clin Invest. 2020;130(5):2620-9. http://doi.org/10.1172/JCI137244

PMid:32217835

26. Wenzhong L, Hualan L. COVID-19: Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Human Heme Metabolism, ChemRxiv; 2020. Available from: https://www.chemrxiv.org/engage/chemrxiv/article-details/60c74fa50f50db305139743d. [Last accessed on 2021 Dec 25].

27. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020;395(10229):1054-62. http://doi.org/10.1016/S0140-6736(20)30566-3

PMid:32171076

28. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, *et al.* Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis. 2020;13:101623. http://doi.org/10.1016/j.tmaid.2020.101623

PMid:32179124

29. Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in COVID-19 patients. Ann Hematol. 2020;15:1-4.