

Original Articles

Relationship of Serum D-dimer Levels with Severity of COVID-19 Infection in Term Pregnancy and Prediction of Feto-maternal Outcome

SARMIN FERDOUS¹, NILUFAR SULTANA², MAHBUBUR RAHMAN RAZEEB³, FATEMA FAIRUJ SAMAD⁴

Abstract:

Aim: To evaluate the value of D-dimer as a biomarker for disease severity in COVID-19 positive pregnant women and prediction of fetomaternal outcome.

Methods: This cross-sectional study was conducted in Department of obstetrics & gynaecology, Dhaka Medical College Hospital, among the term pregnancy with symptomatic & positive RT-PCR for SARS-CoV-2. Total 100 subjects were selected and allocated into two groups- Group A (Patients with normal D-dimer) and group-B (Patients with raised D-dimer). D-dimer level was detected by standard procedure on the first day of admission by SYSMAX CS-1600 analyser in fibrinogen equivalent unit (FEU) and others investigation were performed. Management was conducted according to hospital protocol. All the information collected in data collection sheet and analyzed using SPSS version-22.

Result: In this study mean age of the patient was 24.2 ± 6.5 years. It was showed, 27.0% cases were found to have raised D-dimer where 73.0% were normal level with mean value $2.14 \mu\text{g/ml}$. It was evident from this study is positive significant association between the D-dimer level and severity of COVID-19. Mean value was 0.79 ig/ml in mild cases, 3.27 ig/ml in moderate disease and 4.89 ig/ml in severe disease. Fetomaternal outcome was better in patients with lower D-dimer level.

Conclusion: Present data concluded that rising D-dimer can aid in predicting severity of COVID-19 pneumonia and there was a significant positive significant association ($r=0.941$; $p=0.001$) between the rising D-dimer and worse fetomaternal outcome.

Key-words: COVID-19, Pregnancy, D-dimer, Perinatal outcome

Introduction:

The coronavirus disease 19 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single stranded positive sense RNA virus belonging to the family of coronavirus. The morbidity and mortality of the global community due to this disease is dramatically increasing from time to time. The majority (95%) of currently infected patients at active cases were mildly infected and the

remain 39,391 (5%) were serious or critical condition related to COVID-19¹. According to the World Health Statistics published in 2020, the COVID-19 pandemic is causing significant loss of life, disrupting livelihoods, and threatening the recent advances in health and progress towards global sustainable development goals. In Bangladesh, COVID-19 infections are being reported from Directorate General of Health Service on daily basis. So far, we have around 38292 cases

1. Consultant, Obs & Gyane, DMCH
2. Sr. Consultant, OBGYN, United Hospital, Dhaka.
3. MO, Kuwait Bangladesh Friendship Govt. Hospital
4. Consultant, Obs & Gyane, DMCH

Address of Correspondence: Dr. Sarmin Ferdous, Consultant, Obs & Gyane, DMCH, Mobile: 01711009921, Email-sarminferdous4@gmail.com

with 544 deaths (28th May, 2020)². Early recognition and rapid diagnosis are essential to prevent transmission and provide appropriate care in time frame.

Clinical and virologic studies that have collected repeated biological samples from confirmed patients demonstrate that shedding of SARS-CoV-2 is highest in the upper respiratory tract (URT) (nose and throat) early in the course of the disease³⁻⁵, within the first 3 days from onset of symptoms. The incubation period for COVID-19, which is the time between exposure to the virus (becoming infected) and symptom onset, is, on average, 5–6 days, but can be up to 14 days. During this period, also known as the “presymptomatic” period, some infected persons can be contagious, from 1–3 days before symptom onset⁶.

More than 80% of infected patients manifest with only mild clinical symptoms⁷, early identifying the risks of an adverse outcome remains the key to optimize management and improve survival. Previous studies found that advanced age and presence of comorbidity (e.g., cardiovascular disease or hypertension) were risk factors associated with an adverse outcome such as admission to intensive care unit (ICU), need for mechanical ventilation, or death^{8, 9}. Pregnancy are more likely to develop severe COVID-19 and a number of pregnancy complications have been observed in COVID-19 patients¹⁰. According to the Centers for Disease Control and Prevention (CDC), there have been around 49,000 cases of pregnant women with COVID-19 in the US to date¹¹. Little is known about the impact of pregnancy on COVID-19 and vice versa. Pregnant women with COVID-19 are more likely to develop severe illness than non-pregnant women, with an increased rate of admission to the intensive care unit, need for supplemental oxygen, ventilation, and mortality¹². In a recent meta-analysis, Dubey et al. found that 27% of pregnant individuals with COVID-19 had adverse pregnancy events such as preterm birth, fetal vascular malperfusion, and premature fetal membrane rupture¹³.

Pregnancy is a complicated physiological process, during which the balance of the hemostatic systems is tipped toward a hypercoagulable state. Compared with the non-pregnant women, the maternal D-dimer levels are significantly elevated indicating increased thrombin activity and fibrinolysis following fibrin

formation throughout pregnancy¹⁴. Therefore, COVID-19 in pregnancy can accelerate the several adverse event like toxemia in pregnancy, hypertensive disorder or HELLP syndrome. Pre-eclampsia, a pregnancy complication that occurs in around 6–8% of pregnancies, has several overlapping features with COVID-19, including high blood pressure, thrombocytopenia (i.e. low platelet count), and immune dysregulation^{15, 16}. Both hypertension and thrombocytopenia are strong predictors of morbidity and mortality in COVID-19 patients. A higher incidence of fetal vascular malperfusion have been observed in COVID-19 pregnancies, which encompasses thrombosis, poor development of vasculature, and fibrin deposition within the fetal vasculature located within the placenta¹⁷. Some of these pregnancy complications observed may be attributed to the extrapulmonary pathology of COVID-19. Pregnancy enhances the risk of thromboembolic complications due to the increased levels of coagulation factors in the blood¹⁸. Increased D-dimer concentration in COVID-19 patients, indicating degradation of a blood clot, correlates with poorer outcomes¹⁹. COVID-19 may further enhance hypercoagulability in pregnant individuals, putting them at even greater risk for thromboembolism¹⁸.

D-dimers are one of the fragments produced when plasmin cleaves fibrin to break down clots. The assays are routinely used as part of a diagnostic algorithm to exclude the diagnosis of thrombosis. However, any pathologic or non-pathologic process that increases fibrin production or breakdown also increases plasma D-dimer levels. D-dimer elevation upon admission was common and was associated with both increased disease severity and in-hospital mortality in COVID-19²⁰. Therefore, present study was conducted to see the fetomaternal outcome of pregnancy in COVID-19 positive women.

Materials & Methods:

This cross-sectional prospective study was conducted in DMCH. Study subjects were RT-PCR positive COVID-19 term pregnancy admitted for further management. Basic epidemiological data and gynecological anamnesis were taken, as well as the standard laboratory analysis (D-dimer, CBC, AST, ALT, PT, CRP, LDH, S. ferritin, S. creatinine). D-dimer level was detected by standard procedure on the first day of

admission by SYSMAX CS-1600 analyser in fibrinogen equivalent unit (FEU) and others investigation were performed in the Department of Haematology, department of Biochemistry DMCH. Reference ranges for D-Dimers was 483-2256 ng/mL or 0.4-2.25 ig/ml in third trimester¹⁴. Patients were categorized into two groups- Group A (Patients with normal D-dimer) and group-B (Patients with raised or significant D-dimer). The patient kept under followed up daily until discharge from hospital. Management was conducted according to hospital protocol. Severity of disease and outcome were recoded and correlated with admission D-dimer level. All the information collected in data sheet. Data as collected by using a preformed data sheet. Statistical analysis of the data was done using statistical processing software (SPSS) and Microsoft. Quantitative data expressed as mean and standard deviation and qualitative data as frequency and percentage. Comparison was done by tabulation and graphical presentation in the form of tables, pie chart, graphs, bar diagrams, histogram & charts etc.

Result:

Table-I

Age distribution of the study subject (n=100)

Age (years)	Frequency	Percentage
<20	16	16.0
20-25	45	45.0
26-30	26	26.0
>30	13	13.0
Mean $\pm$ SD	23.5 $\pm$ 9.54	

In this study, the age of the patients ranged between 17->35 years. Most of the patients belonged to the age group 20-25 years (42.0%). Mean age was 23.5 $\pm$ 9.54 years.

Table-II

Distribution of cases according to residence (n=100)

Residence	Frequency	Percentage
Rural	38	38.0
Urban	62	62.0

Table showed area of residence of the participants. Large numbers of respondents came from urban area (62.0%), followed by rural area (38.0%).

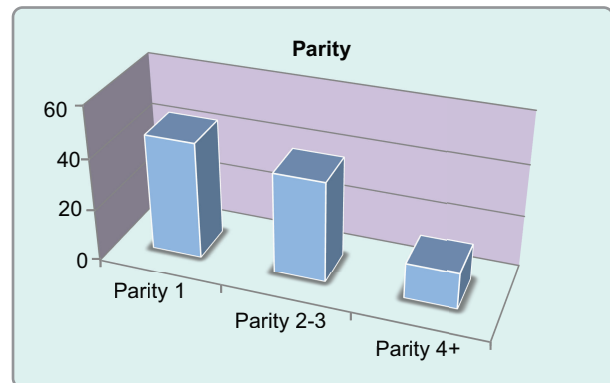


Figure- 1: Obstetrics history (parity) of women (n=100)

Most of the women were primigravida (47.0%). Parity 2 to 3 was 39.0% and multi was 14.0%.

Table-III

Distribution of cases according to clinical manifestation (n=100)

Clinical manifestation	Frequency	Percentage
Fever	79	79.0
Cough	36	36.0
Dyspnoea	20	20.0
Headache	16	16.0
Diarrhoea	20	20.0
Tachycardia	29	29.0
RR > 30 breaths/min	21	21.0
SpO ₂		
> 90%	76	76.0
< 90%	24	24.0
Crepitation over lung	21	21.0
Hypotension	9	9.0

*Multiple respondents

Table shows the distribution of cases according to clinical manifestation. Fever and cough were commonest presentation, 79.0% & 36.0% of patients respectively. Other manifestations were headache (16.0%), diarrhea (20.0%), tachycardia in (29.0%) and fast breathing in 21.0% of patients.

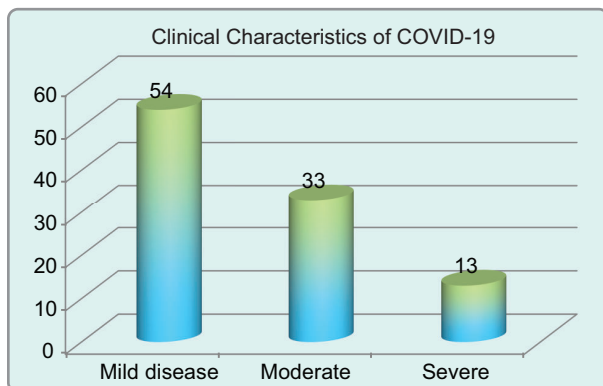


Figure- 2: Clinical characteristics of COVID-19 by severity (n=100)

Figure shows the clinical characteristics of COVID-19 by severity. Symptomatic group with mild cases were 54.0% patients, moderate disease was 33.0% patients and severe was 13.0% of patients.

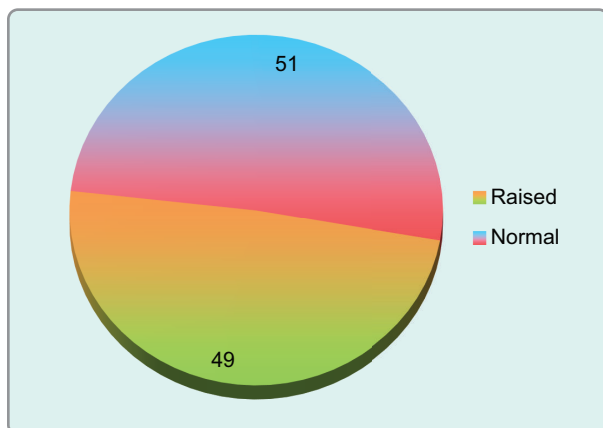


Figure 3: Assessment of D-dimer level in the study population (n=100)

Table shows the D-dimer level in the study population. In this study amongst patients, 49.0% were found to have raised D-dimer where 51.0% were normal level.

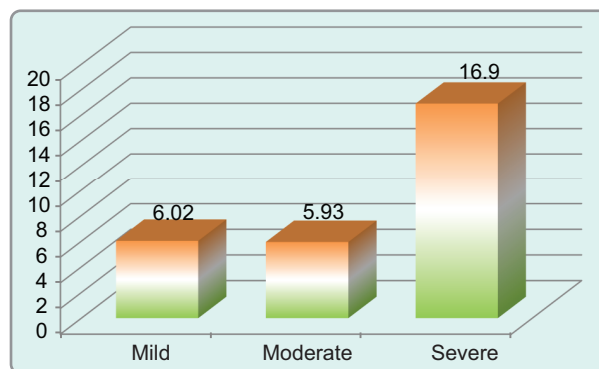


Figure 4: Comparison between D-dimer value versus clinical category of COVID-19 (n=100)

Figure shows the Comparison between D-dimer value versus clinical category of COVID-19. It was evident from this study is positive significant association between the D-dimer level and clinical category of COVID-19. Mean value was 0.79 ig/ml in mild cases, 3.27 ig/ml in moderate disease and 4.89 ig/ml in severe disease

Table shows mode of delivery of pregnant women. On comparison between groups, present study demonstrated that frequency of CS was higher in group-B women (43.2% vs. 75.5% in group A & B respectively). The p value was calculated by chi square test and it was found statistically significant where the level of significance was determined as <0.05.

Table shows maternal complications and outcome. It was found that pre-eclampsia, APH and PROM were predominantly high in group-B patients, 26.5%, 40.8% & 46.9% respectively and difference was statistically significant. Other complications were almost similar in both groups.

Table shows adverse outcome of neonate. It was found that IUGR, preterm delivery, birth asphyxia and neonatal death were predominantly high in group-B patients, and difference was statistically significant.

Table-IV
Mode of delivery of pregnant women (n=100)

Mode of delivery	Group A or normal D-dimer(n = 51)		Group B or raised D-dimer(n = 49)		P value
	No.	%	No.	%	
NVD	29	56.8	12	24.5	0.0041 ^s
CS	22	43.2	37	75.5	
Total	51	100.0	49	100.0	

Table-V
Maternal complications and outcome (n=100)

Maternal outcome	Group A or normal D-dimer(n = 51)		Group B or raised D-dimer(n = 49)		P value
	No.	%	No.	%	
Pre-eclampsia	2	3.92	13	26.5	0.031
APH	9	17.6	20	40.8	0.008
Oligohydramnios	3	5.88	4	8.1	0.728
Polyhydramnios	8	15.6	8	16.3	0.943
GDM	8	15.6	12	24.4	0.085
PROM	12	23.5	23	46.9	0.014
No complication	18	35.2	5	10.2	0.042

Multiple respondents

Table-VI
Neonatal outcome (n=158)

Complication	Group A or normal D-dimer(n = 51)		Group B or raised D-dimer(n = 49)		P value
	No.	%	No.	%	
IUGR	8	15.6	15	30.6	0.027
IUD	3	5.88	4	8.12	0.862
Birth asphyxia	10	19.6	21	42.8	0.028
Preterm birth	5	9.8	11	22.4	0.045
Congenital anomaly	0	0	0	0	-
Neonatal death	2	3.92	9	18.3	0.037

Multiple respondents

Discussion:

The current pandemic with SARS-CoV-2 has already resulted in high numbers of critically ill patients and deaths in the pregnant & nonpregnant population, mainly due to respiratory failure. During viral outbreaks, pregnancy poses a uniquely increased risk to women due to changes to immune function, alongside physiological adaptive alterations, such as increased oxygen consumption and edema of the respiratory tract. The laboratory derangements may be reminiscent of HELLP syndrome, and thus knowledge of the COVID-19 relationship is paramount for appropriate diagnosis and management. In addition to routine measurements of different inflammatory markers, D-dimers, prothrombin time, and platelet count poses great importance in pregnancy. These investigations in SARS-CoV-2-positive pregnant women are vital, as their derangement may signal a more severe COVID-19 infection, and may warrant pre-emptive admission and consideration of delivery to achieve maternal stabilization²¹.

In this study, mean age was 23.5 ± 9.54 years. Most of the women were primigravida (47.0%). Fever and cough were commonest presentation, 79.0% & 36.0% of patients respectively. Other manifestations were headache (16.0%), diarrhea (20.0%), tachycardia in (29.0%) and fast breathing in 21.0% of patients.

Data for 64 pregnant women shows that mean age of the participants was 26.33 ± 5.15 years. Headache & fever occurred significantly among the patients. Non-specific other symptoms such as fever, cough, fatigue, anorexia, weakness, myalgia, sore throat, dyspnoea, nasal congestion, also observed in COVID-19²². Atypical symptoms may occur, especially in people with weakened immunity, elderly people, and pregnant women. Moreover, such COVID-19 infection symptoms as dyspnoea, fatigue, and fever can be confused with the physiological effects of pregnancy^{23, 24}.

In a review of 108 pregnant women with COVID-19, it was reported that women who presented with fever (68%) and cough (34%) in the third trimester²⁵.

Reportedly, 70% of those women had high C-reactive protein, 59% had lymphocytopenia, and 91% delivered by C-section. In another study, symptoms including fever, cough, shortness of breath, and anosmia were found to be significantly associated with COVID-19 in pregnancy²⁶.

Physiological and mechanical changes in pregnancy increase the susceptibility to the infections in general and speed up progression to respiratory failure in pregnant women, especially if the cardiovascular system is affected²⁷. Pregnant women with COVID-19 thus have a risk of developing severe pneumonia. Reportedly, risk profiling, including radiological images and PCR, at the time of admission may improve the chances of risk identification as well as the prognosis in such patients²⁸. Recent study noted that D dimer on admission greater than 2.0 µg/mL (fourfold increase) could effectively predict in hospital mortality in patients with Covid 19, which indicated D dimer could be an early and helpful marker to improve management of Covid 19 patients²⁹.

In this study amongst patients, 49.0% were found to have raised D-dimer where 58.0% were normal level. It was evident from this study is positive significant association between the D-dimer level and clinical category of COVID-19. Mean value was 0.79 ig/ml in mild cases, 3.27 ig/ml in moderate disease and 4.89 ig/ml in severe disease. It was found that pre-eclampsia, APH and PROM were predominantly high in group-B patients (or patients with raised D-dimer), 26.5%, 40.8% & 46.9% respectively and difference was statistically significant. Neonatal outcome revealed that IUGR, preterm delivery, birth asphyxia and neonatal death were significantly high in group-B patients (or patients with raised D-dimer).

Previous study noted that at admission, D-dimer level was above the upper reference limits (mean value 1,727 µg/L)³⁰ in pregnancy third trimester. Laboratory test results examined in a study comparing pregnant and non-pregnant women with positive COVID-19 test results demonstrated significantly higher levels of inflammatory markers such as white blood cell count, neutrophil count, C-reactive protein, procalcitonin, and D-dimer²².

Coagulopathy results from concurrent activation of the coagulation and fibrinolytic cascades, here likely triggered by sepsis, causing clotting factor consumption. Manifestations can be either thrombotic or hemorrhagic. Pregnancy adds further complexity,

given its physiologically hypercoagulable state, with rising coagulation factors, including a fibrinogen and D-dimers increase to 50% above baseline by the third trimester³¹. A mounting amount of evidence is supporting the role of vascular endothelialitis and thrombosis in the pathogenesis of COVID-19³⁰, and D-dimer values above 1000 µg/L have been associated with a poor prognosis³². In our study D-dimer values were above this limit in all the timepoints.

Significantly elevated D-dimers were observed in pregnancy (12-fold to 17-fold upper normal range)²¹. Concerningly, recent reports position elevated D-dimers as a poor prognostic indicator in non-pregnant individuals. Huang et al. noted higher D-dimers in those requiring ICU admission vs. those who did not (median D-dimer 2.4 mg/L (0.6-14.4) vs. 0.5 mg/L (0.3-0.8); $p=0.0042$)³³. Tang et al. observed higher D-dimers in non-survivors vs. survivors [2.12 ug/mL (range 0.8-5.3 ug/mL) vs. 0.6 ug/mL (0.4-1.3 ug/mL)]³⁴. Given the typical D-dimer rise during gestation³¹, it remains unclear what D-dimer threshold would indicate unfavourable prognosis in pregnancy. The ISTH suggests that those with significant D-dimer elevation (arbitrarily defined as a 3-4 fold above upper normal range) be hospitalized even in the absence of other concerning symptoms³⁵.

Previous study highlights a possible link between third-trimester maternal COVID19 infection and rapid maternal deterioration, with progressive coagulopathy. To date, no maternal mortality in COVID19 has been reported; however, as pregnancy may not protect COVID19 patients from coagulopathy, and coagulopathy is linked to poorer prognosis outside of pregnancy, it may presage impending compromise²¹. The described laboratory derangements can be reminiscent of HELLP syndrome, and thus knowledge of the COVID-19 relationship is paramount for appropriate diagnosis and treatment. As per ISTH recommendations, routine measurements of D-dimers, prothrombin time, and platelet count in all patients presenting with COVID19 may aid risk stratification³⁵.

Conclusions:

Present study findings concluded, D-dimer was varied significantly with severity of COVID-19 in obstetric patients and predict the poor fetomaternal outcome, supporting its employment as a tool to monitor the evolution of the disease.

Although COVID infections are not very high now, but still now patients found in tertiary and secondary care hospital with COVID infection in frequently. COVID is not eradicated completely. For this reason, health authority or Government of Bangladesh not declared the COVID free situation. COVID infection is existence in a mild level in Bangladesh. Furthermore, recently a new variant of COVID (The sub-variant, JN.1) detected in Bangladesh. So COVID infection is alarming issue in our country and importance D-dimer as a prognostic marker of COVID-19 is significant in obstetric patients.

References:

1. Gebruj A, Birhanub T, Wendimuc E, Ayalewn A, Mulatd S, Abasimele H, et al. Global burden of COVID-19: Situational analysis and review. *Hum Antibodies* 2021;29(2):139-148.
2. Ferdousi S. National Guidelines on Clinical Management of Coronavirus Disease 2019 (COVID-19). 2020:1-46.
3. Yu P, Zhu J, Zhang Z, Han Y, Huang L. A familial cluster of infection associated with the 2019 novel coronavirus indicating potential person-to-person transmission during the incubation period. *J Infect Dis.* 2020.
4. Huang R, Xia J, Chen Y, Shan C, Wu C. A family cluster of SARS-CoV-2 infection involving 11 patients in Nanjing, China. *Lancet Infect Dis.* 2020;20(5):534-5.
5. Pan X, Chen D, Xia Y, Wu X, Li T, Ou X, et al. Asymptomatic cases in a family cluster with SARS-CoV-2 infection. *Lancet Infect Dis.* 2020;20(4):410-1.
6. Wei WE, Li Z, Chiew CJ, Yong SE, Toh MP, Lee VJ. Presymptomatic Transmission of SARS-CoV-2 - Singapore, January 23-March 16, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(14):411-5.
7. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* 2020; 382:1708–20.
8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020; 395:1054–62.
9. Zhao X, Zhang B, Li P, Ma C, Gu J, Hou P. Incidence, clinical characteristics and prognostic factor of patients with COVID-19: a systematic review and meta-analysis. *medRxiv* [Preprint]. (2020)
10. Moore KM, Suthar MS. Comprehensive analysis of COVID-19 during pregnancy. *BiochemBiophys Res Commun.* 2021;538:180-186.
11. Centers for Disease Control and Prevention. CDC COVID Data Tracker. Data on COVID-19 during Pregnancy: Severity of Maternal Illness. <https://covid.cdc.gov/covid-data-tracker/#pregnant-population>. December 2020.
12. Zambrano L.D., Ellington S., Strid P., Galang R.R., Oduyebo T., Tong V.T., Woodworth K.R., Nahabedian J.F., Azziz-Baumgartner E., Gilboa S.M., Meaney-Delman D. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status — United States, January 22–October 3, 2020. In: Prevention U.D.o.H.a.H.S.C.f.D.C.a., editor. 2020. pp. 1641–1647.
13. Dubey P., Reddy S.Y., Manuel S., Dwivedi A.K. Maternal and neonatal characteristics and outcomes among COVID-19 infected women: an updated systematic review and meta-analysis. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 2020;252:490–501.
14. AldonaSiennicka, Magdalena K³ysz, Kornel Che³stowski, Aleksandra Tabaczniuk, ZuzannaMarcinowska, Paulina Tarnowska, Jolanta Kulesza, Andrzej Torbe, Maria Jastrzębska, "Reference Values of D-Dimers and Fibrinogen in the Course of Physiological Pregnancy: the Potential Impact of Selected Risk Factors—A Pilot Study", *BioMed Research International*, vol. 2020, Article ID 3192350, 12 pages, 2020.
15. Ciobanu A.M., Colibaba S., Cimpoca B., Peltecu G., Panaitescu A.M. Thrombocytopenia in pregnancy. *Maedica (Bucur)* 2016;11:55–60.
16. Lockwood C.J., Yen C.F., Basar M., Kayisli U.A., Martel M., Buhimschi I., Buhimschi C., Huang S.J., Krikun G., Schatz F. Preeclampsia-related inflammatory cytokines regulate interleukin-6 expression in human decidual cells. *Am. J. Pathol.* 2008;172:1571–1579.

17. Smithgall M.C., Liu-Jarin X., Hamele-Bena D., Cimic A., Mourad M., Debelenko L., Chen X. Third-trimester placentas of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive women: histomorphology, including viral immunohistochemistry and in-situ hybridization. *Histopathology*. 2020
18. Benhamou D., Keita H., Ducloy-Bouthors A.S. Coagulation changes and thromboembolic risk in COVID-19 obstetric patients. *Anaesth Crit Care Pain Med*. 2020;39:351–353.
19. Figliozzi S., Masci P.G., Ahmadi N., Tondi L., Koutli E., Aimo A., Stamatelopoulos K., Dimopoulos M.A., Caforio A.L.P., Georgiopoulos G. Predictors of adverse prognosis in COVID-19: a systematic review and meta-analysis. *Eur. J. Clin. Invest*. 2020;50
20. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *J ThrombHaemost*. 2020;18(6):1324-1329.
21. Koumoutsea EV, Vivanti A, Shehata N, Benachi A, Gouez A, Desconclois C et al. COVID-19 and acute coagulopathy in pregnancy. *J ThrombHaemost* 2020 Jul;18(7):1648-1652.
22. Uzel K, Lakhno I. PCR positivity and D-dimer levels in pregnant women with COVID-19. *Clinical and Experimental Obstetrics & Gynecology* ; 47(5):638-644, 2020.
23. Tetikkurt C.: "Respiratory physiology in pregnancy". *Cerrahpa'a Tip Derg.*, 2000., 31, 118-122.
24. Guan W.J., Ni Z.Y., Hu Y., Liang W.H., Ou C.Q., He J.X., et al.: "Clinical characteristics of Coronavirus Disease 2019 in China". *N. Engl. J. Med.*, 2020, 382, 1708-1720.
25. Zaigham M., Andersson O.: "Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies". *Acta. Obstet. Gynecol. Scand.*, 2020, 99, 823-829.
26. Ruggýero M., Somýglýana E., Tassýs B., Pýány L.L.I., Renterýa S.U., Barbara G., et al.: "Covid-19 in the second half of pregnancy: prevalence and clinical relevance". Preprint from Research Square., 2020. Available from: <https://doi.org/10.21203/rs.3.rs-34492/v1>. [Preprint]
27. Dashraath P., Wong J.L.J., Lim M.X.K., Lim L.M., Li S., Biswas A., et al.: "Coronavirus disease 2019 (COVID-19) pandemic and pregnancy". *Am. J. Obstet. Gynecol.*, 2020, 222, 521-531.
28. San-Juan R., Barbero P., Fernández-Ruiz M., López-Medrano F., Lizasoain M., Hernández-Jiménez P., et al.: "Incidence and clinical profiles of COVID-19 pneumonia in pregnant women: a single-center cohort descriptive study from Spain". *Lancet*, 2020, 23, e100407.
29. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *J ThrombHaemost*. 2020;18(6):1324-1329.
30. Lombardi, A., Duiella, S., Li Piani, L. et al. Inflammatory biomarkers in pregnant women with COVID-19: a retrospective cohort study. *Sci Rep* 11, 13350 (2021)
31. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. *Obstet Gynecol*. 2009; 114: 1326-31.
32. Zhou, F. et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet* 395, 1054–1062 (2020).
33. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020; 395: 497-506.
34. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J ThrombHaemost*. 2020.
35. JeckoThachil NT, Satoshi Gando, Anna Falanga, Marco Cattaneo, Marcel Levi, Cary Clark, Toshiaki Iba. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. 2020.