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The Potential Role of Hematological and Biochemical Parameters in Pregnant Women with Viral Infection

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ABSTRACT

Objective: Pregnancy is a process in which not only physical changes occur, but also immune responses are modulated. Therefore, pregnant women are more susceptible to viral infections due to these changes during the pregnancy. The present study aimed to evaluate the hematological and biochemical parameters of pregnant women diagnosed with viral infection.

Materials and Methods: The study groups consisted of pregnant women diagnosed with cytomegalovirus (CMV), hepatitis B virus (HBV), influenza, Covid-19 and healthy pregnant women as control group. The data of a total of 522 pregnant women were analyzed retrospectively. SPSS 22.0 statistics package program was used for data analysis.

Results: Significant differences were found in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, and neutrophil counts between CMV and control groups. There were also significant differences in AST, ALT, red blood cell distribution width (RDW), neutrophil lymphocyte ratio (NLR), white blood cell (WBC), platelet (PLT), neutrophil and lymphocyte values between hepatitis B surface antigen (HBsAg) positive and HBsAg negative pregnant groups. NLR and basophil (BASO) % of pregnant women with influenza infection were significantly higher than the control group. In Covid-19 positive pregnant women, AST, ALT, WBC, BASO values and BASO% were found to be significantly different from the control group. In addition, WBC and NLR values in Covid-19 positive pregnant women were found to be significantly lower than the influenza group.

Conclusion: All these results suggest that especially the NLR value may have diagnostic and prognostic significance for viral infections in pregnant women. However, studies with larger samples and prospective analyses are needed for stronger evidence.

Keywords: Viral infection, neutrophil lymphocyte ratio, pregnancy, retrospective

INTRODUCTION

Pregnant women are at high risk for viral infections and related complications due to the physiological and immunological changes during pregnancy. The adaptation of the immune system to tolerate the allogeneic fetus in this process is among the main reasons for these changes (1).

Cytomegalovirus (CMV) is one of the common congenital contagious infections. Serological screening test is performed during pregnancy for the diagnosis of primary infection of CMV. However, detection of DNA for CMV by amniocentesis is considered as the gold standard for diagnosis in the estimation of primary infection. CMV infection can cause serious sequelae such as neurological

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disability, hearing loss and vision loss in new-borns. Although the primary infection during pregnancy is asymptomatic in most of the mothers, care should be taken because of the sequelae that may occur later in the newborn (2).

Another issue that may pose a serious risk for both mother and fetus during pregnancy is hepatitis B virus (HBV) infection. HBV infection carries serious risks for the mother, especially in the second trimester and during delivery. In addition, pregnant women with high viremia are at risk of mother-to-child transmission of HBV (3). For this reason, follow-up during pregnancy and postpartum against pregnancy-associated hepatitis B reactivation is of great importance.

On the other hand, the literature contains various information regarding the influenza virus infection, which caused pandemics in the past due to its rapid spread potential, affecting both maternal health and pregnancy outcome. The study results implied that disease severity was associated with preterm birth and stillbirth. The fact that pregnant women are more susceptible to flu-related complications has been attributed to immunological (changes in T and B cell counts) and physiological adaptations (increased respiratory rate and intra-abdominal pressure) during pregnancy (4).

Nowadays, the Covid-19 pandemic, which affected millions of people, was experienced. The main symptoms of Covid-19 such as fever, cough and shortness of breath have clinical manifestations similar to influenza (5). Some hematological parameters have been reported and can serve as diagnostic and prognostic markers depending on Covid-19 severity (6).

In the fight against viral infections, including influenza and Covid-19, anti-viral treatments and vaccinations can help to prevent negative pregnancy outcomes. However, information on the adverse effects of vaccines and antiviral treatments on mother and baby is limited. In this context, it is critical to detect viral infections before they pose a threat to maternal and infant health.

This study aimed to evaluate the relationship between viral infections during pregnancy and pregnant women's hematological and biochemical parameters.

MATERIALS AND METHODS

Istanbul Medeniyet University Goztepe Training and Research Hospital, Clinical Research Ethics Committee approval was obtained for this study (Date: 10.02.2021, Decision No: 2021/0140).

Data Collection

The present retrospective study aimed to evaluate the hematological and biochemical parameters of pregnant patients diagnosed with viral infection. Data were collected from 555 pregnant patients and 141 healthy pregnant women who attended to the Istanbul Esenler Obstetrics and Pediatrics Hospital and Istanbul Haseki Sultangazi Training and Research Hospital, Gynecology outpatient clinic, between the years 2018 and 2020. Among these, 140 pregnant women with HBV infection, 4 pregnant women with Covid-19 infection and 30 pregnant women with CMV infection were subsequently excluded due to missing data. Pregnant women with gestational diabetes mellitus (GDM), preeclampsia, hypothyroidism, hyperthyroidism, pregnancy-related autoimmune diseases, and different concomitant viral infections were also excluded.

Patients' symptoms at presentation, white blood cell (WBC, 10^3/µL) count, red blood cell (RBC, 10^{12}/L) count, platelet (PLT, 10^3/µL) count, mean platelet volume (MPV, fL), platelet distribution width (PDW, %), neutrophil (NEU, 10^3/µL) count and percent, basophil (BASO, 10^3/µL) count and percent, eosinophil (EOS, 10^3/µL) count and percent, monocyte (MONO, 10^3/µL) count and percent, lymphocyte (LYM, 10^3/µL) count, red blood cell distribution width (RDW, %), alanine aminotransferase (ALT, U/L), aspartate aminotransferase (AST, U/L) and neutrophil lymphocyte ratio (NLR) were evaluated. Routine blood tests were performed using the fluorescence flow cytometry (FFC) method and an automated hematology analyzer (Sysmex XN-1000). Using an automated biochemical analyser, AST and ALT parameters were measured by the enzymatic colorimetric method, and vitamin D (ng/mL) was determined by paramagnetic particle chemiluminescent immunoassay (Beckman Coulter AU680). Anti-CMV IgG and HBsAg were analyzed by chemiluminescent microparticle immunoassay (CMIA) (Architect i2000SR and Architect i1000, Abbott).

Statistical Analyses

The IBM SPSS Statistics 22 program was used for statistical analysis of this study. The distribution of variables was evaluated with Kolmogorov-Smirnov and Shapiro Wilks tests. Student's t test was used to compare normally distributed variables, and the Mann-Whitney U test was used to compare non-normally distributed continuous variables. The correlation between the NLR value and gestational week were determined by the Spearman's correlation test. The Pearson's correlation analysis was also used to evaluate the relationship between vitamin D and ALT levels. Statistical significance was taken as p-values less than 0.05.

RESULTS

CMV Infection

The first group consisted of 53 CMV positive and 141 CMV negative pregnant women. The mean age of the CMV and control groups was 28.6 ± 5.2 and 29.2 ± 4.3, respectively ($p>0.05$). In this study group, WBC, NEU, LYM, AST and ALT values, which are routine blood parameters of pregnant women, were evaluated retrospectively. AST and ALT values of the pregnant group with CMV infection were found to be statistically significantly higher than the CMV negative control group. While no significant difference was observed in WBC and LYM values, the NEU value was found to be significantly lower than the control group. The other parameters are presented Table 1.

Table 1. Comparison of CMV and control groups.

	CMV (n=53)	Control (n=141)	p-value
AST	29.68 ± 24.92	18.36 ± 32.9	[2]0.001*
ALT	14.16 ± 3.75	12.22 ± 18.56	[2]0.000*
WBC	10.16 ± 4.04	10.14 ± 3.09	[2]0.744
NEU	67.06 ± 8.51	70.16 ± 13.59	[2]0.019*
LYM	21.68 ± 8.37	20.45 ± 7.13	[1]0.463

Cytomegalovirus (CMV), aminotransferase (AST), alanine aminotransferase (ALT), white blood cell (WBC), neutrophil (NEU), lymphocyte (LYM), [1]Student t Test, [2]Mann Whitney U Test, all values are shown as mean ± SD, SD: Standard deviation, *p<0.05

Table 2. Comparison of HBsAg positive and HBsAg negative groups.

	HBsAg (+) (n=135)	HBsAg (-) (n=66)	p-value
MPV	9.72 ± 0.86	9.78 ± 1.41	[1]0.715
AST	24.25 ± 7.27	16.21 ± 4.95	[1]0.000*
ALT	15.6 ± 9.89	13.46 ± 8.2	[2]0.007*
RDW	13.6 ± 3.98	14.17 ± 1.42	[2]0.000*
PDW	10.69 ± 1.56	16.14 ± 1.57	[1]0.000*
NLR	1.59 ± 1.39	3.55 ± 1.42	[1]0.000*
Vitamin D	16.49 ± 6.56	19.44 ± 9.14	[1]0.194
WBC	8.48 ± 2.13	9.51 ± 2.43	[2]0.003*
PLT	306.63 ± 75.59	246.34 ± 83.38	[1]0.000*
NEU	4.67 ± 4.18	6.70 ± 2.34	[2]0.000*
LYM	3.19 ± 1.02	2.03 ± 0.57	[2]0.000*

Mean platelet volume (MPV), aminotransferase (AST), alanine aminotransferase (ALT), red blood cell distribution width (RDW), platelet distribution width (PDW), neutrophil lymphocyte ratio (NLR), white blood cell (WBC), platelet (PLT), neutrophil (NEU), lymphocyte (LYM), [1]Student t Test, [2]Mann Whitney U Test, all values are shown as mean± SD, SD: Standard deviation, *p<0.05

Hepatitis B Surface Antigen (HBsAg) Infection

Group 2 consisted of 135 HBsAg positive and 66 HBsAg negative pregnant women. The mean age of the influenza and control groups was 27.2 ± 4.7 and 26.3 ± 4.9, respectively (p>0.05). The NLR was calculated from these parameters. While the WBC and NEU values of the HBsAg positive pregnant group were statistically significantly lower than the healthy control group, the LYM value was found to be higher, and accordingly, the NLR value was significantly lower (Table 2). In addition, RDW, PLT and PDW values were found to be significantly different in HbsAg positive pregnant women (p<0.001). AST and ALT values in the patient group were also higher than the control group (p<0.01). However, no statistically significant difference was observed between the HBsAg positive and negative control groups in terms of vitamin D values (Table 2). No correlation was also found between the vitamin D and ALT in both groups (r=-0.316; p=0.153 in control, r=0.173; p=0.344 in HbsAg positive).

Influenza Infection

The third group consisted of 63 influenza positive and 67 healthy pregnant women. The mean age of the influenza and control groups was 28.4 ± 6.0 and 28.8 ± 5.5, respectively (p>0.05). WBC, RBC, PLT, NEU, LYM, EOS, BASO, NEU%, LYM%, EOS%, BASO% values of this group were evaluated retrospectively. In addition, LYM x PLT and NLR values were calculated. BASO% values (p<0.001) and NLR values (p<0.01) of the pregnant group with influenza infection were found to be statistically significantly higher than the control group. A more detailed description of the data is given in Table 3. In influenza-infected pregnant women, a weak correlation was also observed for the NLR value and gestational week (r=0.279; p<0.05).

Covid-19 Infection

In the last group, there were 130 Covid-19 positive and 67 negative pregnant women. The mean age of the influenza and control groups was 26.3 ± 4.2 and 28.8±5.5, respectively

Table 3. Comparison of influenza and control groups.

	Influenza (n=63)	Control (n=67)	p-value
Age	28.43 ± 6.06	28.88 ± 5.54	[1]0.666
WBC	9.85 ± 3.06	9.96 ± 3.25	[2]0.608
RBC	4.19 ± 0.42	4.19 ± 0.49	[1]0.945
PLT	237.64 ± 55.77	237.34 ± 82.2	[2]0.483
NEU	7.4 ± 2.5	7.21 ± 3.35	[2]0.422
LYM	2.1 ± 0.92	1.97 ± 0.62	[2]0.837
EOS	0.19 ± 0.16	0.12 ± 0.09	[2]0.328
BASO	0.02 ± 0.02	0.04 ± 0.13	[2]0.858
NEU%	71.69 ± 9.93	71.11 ± 10	[2]0.610
LYM%	19.31 ± 8.84	21.76 ± 8.59	[2]0.060
EOS%	2.13 ± 2.18	1.39 ± 1.3	[2]0.494
BASO%	0.48 ± 0.32	0.23 ± 0.14	[2]0.000*
LYMxPLT	512.07 ± 314.32	481.15 ± 242.09	[2]0.973

White blood cell (WBC), red blood cell (RBC), platelet (PLT), neutrophil (NEU), lymphocyte (LYM), eosinophil (EOS), basophil (BASO), [1]Student t Test, [2]Mann Whitney U Test, all values are shown as mean± SD, SD: Standard deviation, *p<0.05

(p<0.05). AST, ALT, WBC, PLT, NEU, LYM, EOS, BASO, NEU%, LYM%, EOS%, BASO% parameters of the pregnant women were evaluated retrospectively. AST (p<0.001) and ALT (p<0.01) values of pregnant women with Covid-19 infection were found to be statistically significantly higher than the healthy control group (Table 4). In addition, BASO (p<0.001), BASO% (p<0.05) values were found to be statistically significant higher and WBC values (p<0.01) were lower in pregnant women with Covid-19 infection. The detailed information is shown in Table 4. The Covid-19 infection group was also compared with the influenza group (Table 5). Finally, Table 6 summarizes the parameters with significant differences and related groups.

DISCUSSION

This study aimed to examine the hematological and biochemical parameters of pregnant women who had viral infections during pregnancy such as CMV, HBV, Influenza and Covid-19. The first group consisted of CMV, one of the most common congenital infections. While no difference was found in WBC counts in this group, significant differences were found in ALT, AST and NEU values. CMV-associated infection in fibroblast and macrophage cells causes activation of the nuclear factor kB (NF-kB) (7). NF-κB, is responsible for the activation of various cytokines, and may also be associated with the increase in ALT and AST levels in CMV infection (8).

In the study by Nigro et al., ALT, AST and LYM% were found to be higher in pregnant women with primary and recurrent CMV infection compared to the control group. Accordingly, an increase in AST and at least 40% LYM may indicate the presence of primary CMV infection (9). Interestingly, although a significant increase in ALT and AST values was detected in this study, the increase in LYM% was not significant.

The effects of pregnancy on chronic HBV infection (CHB) or the effects of HBV infection on pregnancy are not clearly known. However, it is possible that changes in the immune system during pregnancy allow for greater viral replication in individuals with chronic HBV. Detection of HBsAg is one of the main serological markers of acute and chronic hepatitis B (10). However, some values in routine blood parameters may also give clues about infection. In this study, AST and ALT values of the HBsAg positive pregnant group were found to be statistically significantly higher than the healthy control group, and these values are consistent with the literature. In addition, several studies have reported high RDW levels in CHB patients (11-13). It has been noted that viral load can have a significant effect on RDW when ALT levels are more than 2 times higher than in the normal group (14). High RDW is positively associated with the severity of CHB disease and may be a determining factor in the follow-up of patients with liver cirrhosis (11-13). Although the increase in ALT levels in this study altered significantly, there was no two-fold difference compared to the control group. Interestingly, the RDW values of the HBsAg positive pregnant group were significantly lower than the control group. Conflicting results regarding the RDW value may be due to different cohorts. On the other hand, anemia and, nutrition, folate and B12 deficiencies in pregnancy may also be the reason for these differences.

Table 4. Comparison of Covid-19 positive and control groups.

	Covid-19 (n=130)	Control (n=67)	p-value
Age	26.36 ± 4.17	28.88 ± 5.54	[1]0.003*
AST	28.55 ± 33.3	16.76 ± 5.21	[2]0.000*
ALT	25.08 ± 52.69	13.97 ± 9.46	[2]0.002*
WBC	8.64 ± 3.39	9.96 ± 3.25	[2]0.001*
PLT	237.78 ± 85.49	237.34 ± 82.2	[2]0.977
NEU	10.59 ± 16.59	7.21 ± 3.35	[2]0.067
LYM	3.1 ± 5.25	1.97 ± 0.62	[2]0.091
EOS	0.19 ± 0.36	0.12 ± 0.09	[2]0.119
BASO	0.038 ± 0.15	0.037 ± 0.13	[2]0.000*
NEU%	65.71 ± 18.06	71.11 ± 10	[2]0.087
LYM%	21.44 ± 10.18	21.76 ± 8.59	[2]0.858
BASO%	0.31 ± 1.03	0.23 ± 0.14	[2]0.026*

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), white blood cell (WBC), platelet (PLT), neutrophil (NEU), lymphocyte (LYM), eosinophil (EOS), basophil (BASO), [1]Student t Test, [2]Mann Whitney U Test, all values are shown as mean± SD, and median values are presented in brackets, SD: Standard deviation, *p<0.05.

Table 5. Comparison of Covid-19 positive and influenza groups.

	Covid-19 (n=130)	Influenza (n=63)	p-value
PLT	237.78 ± 85.49	237.64 ± 55.77	[2]0.459
MPV	10.15 ± 1.14	9.51 ± 1.87	[1]0.371
PDW	14.35 ± 2.43	15.08 ± 1.77	[2]0.599
NEU	10.59 ± 16.59	7.4 ± 2.5	[2]0.330
EOS	0.19 ± 0.36	0.19 ± 0.16	[2]0.258
NEU%	65.71 ± 18.06	71.69 ± 9.93	[2]0.041*
EOS%	1.27 ± 1.49	2.13 ± 2.18	[2]0.251
WBC	8.64 ± 3.39	9.85 ± 3.06	[2]0.002*
RBC	3.98 ± 0.55	4.19 ± 0.42	[1]0.008*
LYM	3.1 ± 5.25	2.1 ± 0.92	[2]0.480
MONO	0.96 ± 1.74	6.55 ± 3.03	[2]0.000*
BASO	0.04 ± 0.15	0.02 ± 0.02	[2]0.238
LYM%	21.44 ± 10.18	19.31 ± 8.84	[2]0.111
BASO%	0.31 ± 1.03	0.48 ± 0.32	[2]0.000*
MONO%	6.16 ± 2.54	5.83 ± 2.41	[2]0.746

Platelet (PLT), mean platelet volume (MPV), platelet distribution width (PDW), neutrophil (NEU), eosinophil (EOS), white blood cell (WBC), red blood cell (RBC), lymphocyte (LYM), monocyte (MONO), basophil (BASO), [1]Student t Test. [2]Mann Whitney U Test, all values are shown as mean± SD, and median values are presented in brackets, SD: Standard deviation,*p<0.05

Table 6. Representation of the parameters with significant differences in study groups.

	Group I			Group II	Group III
	CMV	**Influenza**	**Covid-19**	**Hepatitis B**	**Covid-19**
AST	+	NC	+	+	NC
ALT	+	NC	+	+	NC
WBC	-	-	+	+	+
RBC	NC	-	NC	NC	+
NEU	+	-	-	+	-
NEU%	NC	-	-	NC	+
BASO	NC	-	+	NC	-
BASO%	NC	+	+	NC	+
RDW	NC	NC	NC	+	NC
PDW	NC	NC	NC	+	-
NLR	NC	NC	NC	+	NC
PLT	NC	-	-	+	-
LYM	-	-	-	+	-

Significant ones are indicated with plus, non-significant ones are indicated with minus. NC: not-compared. Group I: CMV vs Control, Influenza vs Control and Covid-19 (+) vs Control; Group II: HBsAg (+) vs HBsAg (-); Group III: Covid-19 (+) vs Influenza. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), white blood cell (WBC), red blood cell (RBC), neutrophil (NEU), basophil (BASO), red blood cell distribution width (RDW), platelet distribution width (PDW), neutrophil lymphocyte ratio (NLR), lymphocyte (LYM), CMV (Cytomegalovirus)

Moreover, the PLT value was found to be significantly higher and the NLR value to be lower in pregnant women with HBV in this study. Recently, the NLR value, which can be easily detected from peripheral blood, has attracted attention as a marker of systemic inflammation. Atay et al. found an increase in NLR rates in the CHB group compared to the controls and in the advanced fibrosis group compared to the mild fibrosis group (15). However, in some recent studies, PLT values were found to be higher in CHBs without cirrhosis and liver failure, and lower NLR values compared to controls (13,16-18). Although it is thought that the increase in the NLR value may be associated with poor prognosis and survival, according to studies conducted with various diseases, the results have not been sufficiently clarified.

The detection of NLR may also play an important role in the fight against Covid-19 and influenza-related infections. Neutrophils show potent antimicrobial effects as important components of the leukocyte population. In addition to triggering the release of multiple cytokines to fight infections, they increase the production of reactive oxygen species (ROS) that can result in tissue damage. Although the antiviral responses of neutrophils are not well known, they are immune effector cells that play a primary role in viral infection sites (19). Routine laboratory findings of pregnant women and other adult patients in the early period of Covid-19 infection are contradictory. However, most of them have normal or decreased WBC, high NLR value and lymphocytopenia (6, 20, 21). The NLR value can be a prognostic biomarker and was reported in various studies including patients with non-severe, mild and severe Covid-19 infections (22, 23). In addition, a meta-analysis showed that individuals with severe Covid-19 have a higher NLR than non-severe ones (24). In various studies conducted in our country, high NLR values have been reported in individuals with severe Covid-19. NLR has attracted attention as a predictive factor for Covid 19 diagnosis, prognosis, and survival (25-27). Yılmaz et al. reported that WBC, NEU and LEU values were significantly lower in Covid 19 positive pregnant women compared to negative ones, but they did not find a significant difference in NLR values (28). However, the NLR value showed significant differences when evaluated according to disease severity (28, 29). On the other hand, a retrospective analysis of a large cohort revealed that the NLR values in the first, second and third trimesters of pregnancy may vary (30). In this context, it is important to know in which trimester the pregnant woman is during the measurement of NLR values. In this study, the WBC count was found to be significantly lower between Covid-19 and control groups, while the increase in NLR and LYM values and the decrease in LYM and NEU percentages were not significant. The reason for this may be asymptomatic or mild symptoms of the disease, or the study group may be composed of pregnant

women in different trimesters. Mild thrombocytopenia, liver enzymes (i.e. ALT and AST), lactate dehydrogenase and C-reactive protein (CRP) are also likely to increase in the early period of Covid-19 infection (31). Less common symptoms, according to the laboratory findings of Guan et al., include elevated ALT, AST, and creatine kinase levels (21). In this study, high AST and ALT values were observed in the pregnant group with Covid-19 infection compared to controls.

On the other hand, the clinical symptoms of Covid-19 and influenza are quite similar. In this context, the data of pregnant patients with Covid-19 and flu were also analyzed to determine the distinguishing parameters in the study. The results obtained from various studies have shown that the NLR and WBC values are remarkably lower in Covid 19 individuals than in the influenza group (5, 26, 32). Consistent with other studies, NLR and WBC values were significantly decreased in pregnant women with infection due to the presence of Covid-19 in this study.

There are 5 subtypes of white blood cells, the number of which increases significantly during infection, consisting of neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Unlike the study by Kazancıoğlu et al., a significant increase in BASO and BASO% values were observed in Covid-19 pregnant women in this study (26). Basophils are relatively rare leukocytes that contribute to allergic inflammations due to their ability to migrate from the blood to various other tissues. In addition, there are studies showing that basophils have the capacity to produce Th2-type cytokines and the ability to initiate Th2 immunity (33). In other studies, it has been reported that basophils were decreased during acute disease but were returned to normal after a few days. It has been suggested that basophil counts, which decrease at the beginning of the disease and change afterward, may be an important prognostic marker (34).

CONCLUSION

Immunomodulation, which mediates tolerance of the allogeneic fetus during pregnancy, may render the pregnant woman more susceptible to viruses. According to this study, WBC values were decreased in Covid-19 positive pregnant women, and BASO% and BASO were increased. However, data on the variation of the basophil values due to viral infections are limited. In addition, the WBC, RBC, NEU%, MONO and BASO values of pregnant women with Covid-19 were lower than those with influenza infection. Finally, in line with the literature, high AST and ALT values in the CMV infected group and increased AST, ALT, PLT and RDW values in HBsAg positive patients may help the prediction of infections. Although these changes in blood parameters give clues about the presence of infection, they are not sufficient to be a distinctive pattern of disease. To understand the hematological and biochemical data relation, the study needs to be improved with various larger patient groups.

LIMITATIONS

Since this study was evaluated retrospectively, demographic data of pregnant women such as body mass index, weight averages and pregnancy complications could not be obtained. Chronic or acute infection information of pregnant women with HBV infection could not be obtained either.

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Ethics Committee Approval: The study protocol was approved from the ethical committee of the Istanbul Medeniyet University Goztepe Training and Research Hospital, Clinical Research Ethics Committee (Decision No: 2021/0140).

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