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Original Article

Comparing Placental Histology of Vaccinated and Unvaccinated Pregnant Women During Active Coronavirus Disease 2019 Infection

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ABSTRACT

Objective: We aim to compare the placental histology of vaccinated and unvaccinated women who delivered during active coronavirus disease 2019 infection.

Methods: Forty-two patients were enrolled to study, regardless of coronavirus disease 2019 severity, and they were divided into 2 groups according to their coronavirus disease 2019 vaccination status. Twenty-three patients who were vaccinated in the last 3-6 weeks were classified as a vaccinated group, and 19 patients who had not taken any coronavirus disease 2019 vaccination were classified as an unvaccinated group.

Results: The rate of existence of maternal vascular malperfusion features was significantly higher in the unvaccinated group compared to that of the vaccinated group. Decidual arteriopathy, accelerated villous maturation, increased syncytial knotting, perivillous fibrin plaque, and massive perivillous fibrin deposition were analyzed as maternal vascular malperfusion features. The most common maternal vascular malperfusion feature was decidual arteriopathy in both groups (73.6% in unvaccinated group and 22.7% vaccinated group). In the unvaccinated group, the rate of the existence of at least one of maternal vascular malperfusion features was 100%.

Conclusion: The higher rate of features of maternal vascular malperfusion of placental bed was detected in the placentas of unvaccinated pregnant women with coronavirus disease 2019 infection compared to that in the placentas of vaccinated pregnant women with acute coronavirus disease 2019 infection regardless of disease severity.

Keywords: COVID-19, infections, obstetrics, placenta, pregnancy

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is the most recent deadly pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. Although its spread has diminished after the first quarter of 2022 mainly due to vaccination, it is still an important health concern because of the emergence of the novel variants of the SARS-CoV-2.[1] The impact of COVID-19 infection on pregnant women has been of particular interest to healthcare providers and patients. Data from the literature have supported the idea of COVID-19 infection during pregnancy is associated with a higher rate of fetal death, preterm birth, emerged cesarean delivery, and preeclampsia.[2-4]

SARS-CoV-2 may cause immune system alterations such as overproduction of proinflammatory cytokines, numerical and functional anomalies of T cells, and antigen presentation pathway over activity.[5] Therefore, the placenta can be altered by dysregulated immune status during COVID-19 infection apart from the direct damage of virus replication.[6] Although there are no pathognomonic histological patterns in the placentas of women after COVID-19 infection, a higher rate of maternal vascular malperfusion (MVMP) of the placenta, which was

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recognized by many pathological changes, such as perivillous and intervillous fibrin deposition, decidual vasculopathy, accelerated villous maturation, and increased syncytial knotting, was often detected in women with COVID-19 infection.[7-9] Given these data, the severity of the abnormal placental damage may be the main factor behind the bad obstetrical and neonatal outcomes. Therefore, placental investigations can provide precious information that may be fundamental in improving our knowledge of disease pathogenesis.

Food and Drug Administration (FDA)-approved COVID-19 vaccines have appeared to be safe and effective tools to prevent severe disease, hospitalization, and death against all variants of the SARS-CoV-2 virus.[10] Recombinant mRNA vaccines use lipid nanoparticles with formulation of mRNA fragments.[11] Although an increased number of women have been vaccinated before or during pregnancy, there are no data about the protective effect of COVID-19 vaccination on the abnormal placental histopathology in pregnant women with COVID-19 infection. This study aims to compare the placental histology of vaccinated and unvaccinated women who delivered during active COVID-19 infection.

METHODS

Study Design and Study Groups

This multicenter retrospective study was performed at Private Erciyes Kartal Hospital, Kayseri, Türkiye, and Izmir Private Can Hospital, Izmir, Türkiye between September 2020 and May 2022.

The initial cohort comprised 58 term pregnant women who delivered during active COVID-19 infection. The COVID-19 infection was diagnosed 0-10 days before delivery was defined as COVID-19 infection during delivery. After applying inclusion/exclusion criteria according to patient data, 42 patients were finally enrolled, regardless of COVID-19 severity. The patients were divided into 2 groups according to their COVID-19 vaccination status. Twenty-three patients were vaccinated in the last 3-6 weeks (VG group), and 19 patients were not vaccinated (UVG group). All patients had been vaccinated with BioNTech162b2 (Pfizer) vaccine in their pregnancy.

The median (25%-75%) time interval between COVID-19 infection and delivery was 4 days in both groups. No patient was diagnosed with having severe COVID-19 infection in the VG group. Six patients in the UVG were hospitalized with severe COVID-19 infection for medical and supportive treatment. The non-hospitalized patients were treated symptomatically with paracetamol. All patients in both groups were treated with low-molecular-weight heparin until delivery.

Exclusion criteria for both groups were as follows: being aged older than 40 years or under 18 years (5 patients), non-gestational diabetes (3 patients), hypertensive disease of pregnancy (6 patients), and women who had TORCH group infection seropositivity (2 patients).

Ethical approval was obtained from the Non-interventional Clinical Research Ethics Committee of İzmir Bakırçay University (Decision date: June 22, 2022, approval number: 641). All protocols were conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study for placental evaluation.

Data Collection

The following data were obtained and recorded from the electronic medical records of the patients in both groups: maternal demographics, obstetric history, the time interval between diagnosis of COVID-19 infection and delivery, gestational age at delivery, the history of COVID-19 vaccinations, route of delivery, and the existence of 5 features of MVMP of the placenta, namely decidual arteriopathy, increased syncytial knotting, perivillous fibrin plaque, massive perivillous fibrin deposition, and accelerated villous maturation, from pathological reports of placentas.

The routine pathological examination has been conducted on all placentas of women who delivered with COVID-19 infection since June 2020 in the study hospitals. Gross bleeding and necrosis were observed as a result of macroscopic examination of the placenta. After initial examination, all placentas were sliced at 1-cm intervals on the maternal surface and fixed in 10% buffered formalin solution for 24 hours. Sections enrolled included 2 of the umbilical cord, 2 of the placental membranes, 2 of the fetal surfaces of placenta, 2 of the maternal surfaces of placenta, 2 of the full-thickness sections, and 2 of the suspicious gross lesion areas. Sections underwent routine processing, sliced at 5 μm, and stained with hematoxylin and eosin (H&E). All pathologic investigations were performed by an experienced pathologist using Olympus CX32 microscope.

The diagnosis of COVID-19 was confirmed by oropharyngeal and/or nasopharyngeal swabs by quantitative real-time reverse-transcriptase polymerase chain reaction. After the COVID-19 infection diagnosis, all patients were examined by an obstetrician with the obstetric examination, gray scale ultrasonography, Doppler ultrasonography, and non-stress test. The patients who were in active labor, resembled non-reassuring fetal status and/or with low biophysical profile score, and had severe COVID-19 infection were hospitalized. Non-hospitalized patients were quarantined at home by advising them to pay attention to

fetal movements. Both non-hospitalized and hospitalized patients were evaluated by an obstetrician until delivery in 2-day intervals.

The gestational age of the women was based on the last menstrual period, as verified by measurement of crown-rump length in the first trimester.

Statistical Analysis

The normality of the distribution of continuous variables was tested by the Shapiro–Wilk test. The Student's *t*-test (for normally distributed data) or the Mann–Whitney *U*-test (for non-normally distributed data) was used to compare continuous variables between the 2 groups. Chi-square tests were used to investigate differences between groups in terms of categorical variables. Mean ± standard deviation (mean ± SD) values were used for normally distributed data, and median (25%-75% quartiles) values were used for non-normally distributed data when summarizing descriptive data. Statistical analysis was performed with the Statistical Package for Social Sciences software for Windows version 24.0, and a *P* value of $< .05$ was accepted to demonstrate statistical significance.

RESULTS

A total of 42 patients (19 patients in the UVG group and 23 patients in the VG group) were included in the final analyses. Demographics and other baseline characteristics were similar in both groups (Table 1).

The rate of existence of MVMP features was significantly higher in the UVG group compared to the VG group. Decidual arteriopathy, accelerated villous maturation, increased syncytial knotting, perivillous fibrin plaque, and massive perivillous fibrin deposition were analyzed as MVMP features, and their microscopic images were shown in Figure 1. The deposition of perivillous fibrin plaque is shown in Figure 1A. Placental decidual arteriopathy is the evidence of fibrinoid necrosis of the vessel wall, and its microscopic image is shown in Figure 1B. The microscopic image of the increased syncytial knotting of placenta is shown in Figure 1C. Figure 1D shows accelerated villous maturation of the placenta. The most common MVMP feature was decidual arteriopathy in both groups (73.60% in UVG group and 22.70% VG group). In the UVG group, the rate of existence of at least one of MVMP features was 100%. The comparison of MVMP features of both groups was shown in Table 2. Four babies from the VG group and 3 babies from the UVG group were admitted in the neonatal care unit with transient neonatal tachypnea.

DISCUSSION

This study revealed that the placentas of unvaccinated pregnant women with acute COVID-19 infection represent a significantly higher rate of the features of MVMP compared to the placentas of vaccinated pregnant women with acute COVID-19 infection in the third trimester, regardless of the disease severity.

Features of MVMP were mostly reported in histopathological findings of placentas in pregnant women with COVID-19.[12] Placental MVMP is not a single placental finding seen either grossly or under the microscope but rather represents a group finding such as decidual arteriopathy,

Table 1. Comparison of Sociodemographic and Baseline Characteristics of Patients

	UVC Group (n = 19)	VC Group (n = 23)	
	Mean ± SD	**Mean ± SD**	***P***
Variables			
Age	26.45 ± 4.57	26.43 ± 3.77	.895
	Median [25%-75%]	Median [25%-75%]	
Body mass index (kg/m^2)	25.70 [min: 19.70-max: 24.10]	21.15 [min: 20.20-max: 24.75]	.314
Gravida	2 [min: 1-max: 4]	2 [min: 1-max: 5]	.481
Parity	2 [min: 0-max: 3]	2 [min: 0-min: 4]	.836
Gestational age at delivery	38.50 [min: 37.60-max: 40.20]	38.20 [min: 37.30-max: 40.30]	.318
Time interval between COVID-19 infection to delivery (days)	4 [min: 0-max: 4]	4 [min: 1-max: 5]	.498
	n (%)	**n (%)**	***P***
Route of delivery			
Cesarean	8 (42.10)	10 (43.40)	.762
Vaginal birth	11(57.80)	13 (56.62)	.897

COVID-19, coronavirus disease 2019; SD, standard deviation; UVC, unvaccinated group; VC, vaccinated group.

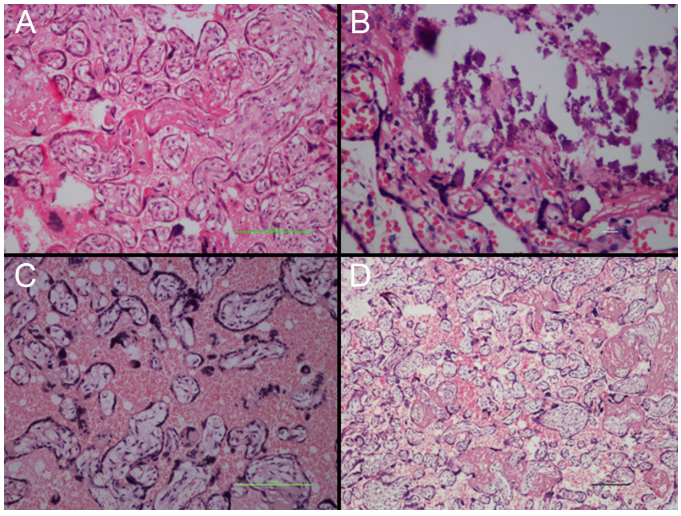

Figure 1. Microscopic images of the placentas (A: perivillous fibrin plaque, B: decidual arteriopathy, C: syncytial knotting, and D: accelerated villous maturation).

accelerated villous maturation, increased syncytial knotting, perivillous fibrin plaque, and perivillous fibrin deposition.[13] Because maternal hypertensive disorders are the major risk factors for MVMP, we excluded the hypertensive patients in this study.[13]

As mentioned before, the SARS CoV-2 should bind to the ACE2 receptor to enter host cells.[4] Although the expression of ACE2 was widely detected in sub-placental syncytiotrophoblast, endothelium, and myometrium in pregnant pigs at early stages of gestation, its density decreases throughout pregnancy, reaching its lowest level in the last trimester.[14] Smithgall et al[15] reported that the placentas of pregnant women having COVID-19 infection showed a higher rate of MVMP features than women who were non-infected, but they did not detect the direct viral presence of SARS-CoV-2 in the placentas by the use of immunohistochemistry and in situ hybridization. Therefore, it is assumed that the placental pathology during COVID-19 infection is caused mainly by infection-associated coagulation and inflammation instead of direct damage of the virus to the placenta.[16]

Table 2. The Comparison of MVMP Features Between UVG and VG Groups

	UVG		VG		
	n	%	n	%	*P*
Decidual arteriopathy	14 of 19	73.6	5 of 23	22.7	**.002***
Increased syncytial knotting	12 of 19	63.1	4 of 23	17.3	**.001***
Perivillous fibrin plaque	13 of 19	68.4	4 of 23	17.3	**.001***
Massive perivillous fibrin deposition	8 of 19	42.1	2 of 23	8.6	**.002***
Accelerated villous maturation	12 of 19	31.5	4 of 23	17.3	**.001***
At least one of MVPM features	19 of 19	100	5 of 23	22.7	**.001***

MVMP, maternal vascular malperfusion; UVC, unvaccinated group; VC, vaccinated group.

In a retrospective study, Shanes et al[17] showed an increased prevalence of having at least one feature of MVMP in 12 of 15 patients, in third-trimester placentas from pregnant women with severe COVID-19 infection compared to controls. They also concluded that the most prominent features of MVMP were decidual arteriopathy including atherosis, mural hypertrophy of arterioles, and intervillous thrombi. In our study, all the studied features of MVMP were higher in the unvaccinated group, decidual arteriopathy being the most encountered lesion. However, we included the patients regardless of disease severity, unlike other study design.

To support the idea that severe disease is not essential for the occurrence of placental damage during COVID-19 infection, Jaiswal et al[18] reported that placentas of asymptomatic or mildly symptomatic COVID-19-positive pregnant women represented significantly higher rates of microscopic findings of placental injury and the features of MVMP compared to COVID-19 negative women. Also, Rebutini et al[19] reported that although it was slightly more frequent among symptomatic patients, the features of MVMP were increased in pregnant women with COVID-19 infection without being related to disease severity. However, some authors claimed that severe COVID-19 infection was associated with more viral accumulation in placenta causing serious placental damage and obstetrical outcomes than non-severe cases.[20,21] In our study, 6 cases (6/19, %31.5) had severe COVID-19 infection according to WHO criteria in the UV group. They were all followed in the first-degree ICU without fetal or maternal mortality, probably malicious care and immediate delivery in non-reassuring fetal status.

The mRNA COVID-19 vaccines have generated a robust humoral and cell-mediated response in pregnant women and are significantly superior to that evoked by COVID-19 infection.[22] Regardless of whether they were pregnant or non-pregnant, vaccinated women gain higher levels of serum antibodies that can neutralize viral particles and non-neutralizing antibodies.[23] Although mRNA vaccines were shown as activating the TLR3 immune response pathway, which had been associated with placental damage and bad obstetrical outcomes in mice, it has been widely confirmed that COVID-19 vaccines were safe and effective with regard to reducing disease transmission

and infection severity in pregnant women.[24,25] In a retrospective controlled study, Shanes et al[26] compared 84 vaccinated women and 116 control women who did not receive a COVID-19 vaccine during pregnancy and concluded that vaccination was not related with increased risk of having placental maternal and fetal malperfusion and placentitis compared with the control group. Also, women with vaccination are more likely to give vaginal birth.[26] Because the study was conducted among pregnant women without COVID-19 infection, no data were reported about the efficacy of vaccination for preventing COVID-19 infection-related placental damage. In our study, we focused on the effect of vaccination on preventing placental damage of acute COVID-19 infection in third-trimester pregnant women.

BioNTech162b2 mRNA (Pfizer) vaccine was allowed by FDA for emergency use in December 2020.[27] In our country, it was introduced for public usage in April 2021, and pregnant women were allowed for vaccination after the 12th gestational week. The vaccine mainly elicits both B- and T-cell responses against the SARS-CoV-2 spike protein.[28] The vaccine uses a potent lipid-nanoparticle delivery system in combination with the use of modified nucleotides, to avoid early activation of interferon-associated genes.[28] In our opinion, although the vaccine could not prevent disease occurrence in all vaccinated pregnant women, it reduces the risk of placental damage by reducing infection-related inflammation.

To the best of our knowledge, this is the first study to compare vaccinated and non-vaccinated pregnant women with regard to COVID-19 infection-related placental damage. However, the limitations of the study include the retrospective nature of research and only the mRNA vaccine being evaluated in this study.

In summary, the higher rate of features of MVMP of placental bed was detected in the placentas of unvaccinated pregnant women with COVID-19 infection compared to that in the placentas of vaccinated pregnant women with acute COVID-19 infection regardless of disease severity. Further randomized trials comparing subgroups of pregnant women, such as pregnant women vaccinated by different vaccine types, are necessary to assess the effects of COVID-19 vaccinations in this context. Although the COVID-19 pandemic has lost its severity, these data can shed light on women's health in future COVID-19 pandemics.

Ethics Committee Approval: Ethics committee approval for this study was obtained from the Non-interventional Clinical Research Ethics Committee of İzmir Bakırçay University (Decision date: June 22, 2022, Approval number: 641).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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