Corner of Academy

Zacharias Fasoulakis*, Asim Kurjak, Ioakeim Sapantzoglou, Anastasia Maria Daskalaki, George Daskalakis and Panos Antsaklis

KANET evaluation in patients with SARS-CoV-2

https://doi.org/10.1515/jpm-2024-0258
Received June 5, 2024; accepted August 2, 2024;
published online August 30, 2024

Abstract

Objectives: To determine a possible correlation between SARS-CoV-2 infection during pregnancy and altered fetal behavior.
Methods: Kurjak's antenatal neurodevelopmental test (KANET) was applied from 28 to 40 weeks in 38 gestations (group A) diagnosed with COVID-19 infection during the first week and 43 non-COVID pregnant women (group B).
Results: No statistically significant differences considering maternal age (33±3.9 years for group A vs. 31±4.1 years for group B) and gestational age (33±1.6 weeks for group A compared to 33±2.1 weeks for group B) were observed. KANET scores were not different between the two groups.
Conclusions: Fetal behavior differences are not altered in women diagnosed with SARS-CoV-2 infection during the third trimester of pregnancy.

Keywords: SARS-CoV-2; fetal neurobehavior; KANET

Introduction

COVID-19, the disease triggered by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as a worldwide pandemic in March 2020 [1]. The physiological changes in the cardiorespiratory and immune systems during pregnancy may make pregnant women and newborns more vulnerable to COVID-19, potentially influencing their response to the infection [2]. There are concerns that fetuses could be exposed to the virus during pivotal stages of development [3]. The impact of COVID-19 on pregnancy outcomes is not well understood, and there is a scarcity of comprehensive meta-analyses on pregnant individuals with the virus. Earlier research, often based on case reports or series, presents challenges in interpretation and could be biased [4, 5]. Findings from a 2020 systematic review indicate that pregnant individuals might not be at higher risk of contracting SARS-CoV-2 or displaying symptoms of COVID-19; however, their risk of experiencing severe symptoms is elevated compared to non-pregnant individuals [5]. Despite recent observational studies indicating possible adverse pregnancy outcomes from both symptomatic and asymptomatic COVID-19 cases, inclusive of mild to severe infections, systematic reviews synthesizing these findings are still lacking [6–12].

Historically, monitoring fetal behavior *in utero* has been crucial for perinatal screening. Advances in ultrasonography over the past few decades have enhanced our understanding of fetal conditions. Prenatal screenings focused on the neurological health of fetuses have provided significant insights, and recent improvements in ultrasound technology have improved the monitoring of fetal physiology in a cost-effective manner with direct visualization [11–13]. The Kurjak's antenatal neurodevelopmental test (KANET), first introduced in 2008, is a sonographic method used to assess fetal neurology and has shown high reliability in evaluating brain function and developmental progress in fetuses. However, data on the use of KANET in pregnancies affected by SARS-CoV-2 remain limited. Studies have shown that prenatal SARS-CoV-2 infection can result in neurodevelopmental and behavioral outcomes, as observed in animal models [1, 2]. This study aims to investigate fetal neurological behavior in pregnant women diagnosed with SARS-CoV-2 using the KANET test. Emerging evidence suggests that SARS-CoV-2 infection during pregnancy could lead to adverse outcomes, such as preeclampsia, preterm birth, and low birth weight. However, the impact of COVID-19 on fetal neurodevelopment remains unclear. This study aims to fill this gap by using the KANET scoring system to assess potential neurological impairments in fetuses exposed to SARS-CoV-2. The study began in

***Corresponding author: Zacharias Fasoulakis**, 1st Department of Obstetrics and Gynecology, National and Kapodistrian University of Athens, Athens, Greece, E-mail: hzaxos@gmail.com. https://orcid.org/0000-0003-0216-3420
Asim Kurjak, Department of Obstetrics and Gynecology, Medical School University of Zagreb, Zagreb, Croatia
Ioakeim Sapantzoglou, Anastasia Maria Daskalaki, George Daskalakis and Panos Antsaklis, 1st Department of Obstetrics and Gynecology, National and Kapodistrian University of Athens, Athens, Greece. https://orcid.org/0000-0002-7760-0608 (I. Sapantzoglou). https://orcid.org/0000-0003-2106-5922 (P. Antsaklis)

December 2019, coinciding with the earliest reports of SARS-CoV-2. Although the pandemic was officially declared in March 2020, early cases were identified globally in late 2019. Initial concerns about potential effects on pregnancy outcomes prompted the early initiation of this study to investigate possible impacts on fetal neurodevelopment [12, 14].

Materials and methods

The Kurjak's antenatal neurodevelopmental test (KANET) was chosen for this study due to its reliability in assessing fetal brain function. Introduced in 2008, KANET evaluates parameters such as isolated head, hand, and leg movements, cranial sutures, hand-to-face/head movements, finger movements, yawning, mouthing, facial expressions, and eye blinking (Figure 1). This test has shown high reliability in evaluating brain function and developmental progress in fetuses. Unlike general movement measurement or the Amiel-Tison neurological assessment, KANET provides a comprehensive sonographic method for prenatal neurological screening. Relevant literature supports its use as a reliable tool for assessing fetal neurodevelopment [5, 6].

A total of 81 pregnant women between 28 to 40 weeks participated in the present study. Participants were subdivided into two groups. The first group (A) included 38 pregnant women with SARS-CoV-2, while the (control) second (B) group included 43 non-COVID pregnant women. The study was performed in the Department of Fetal and Maternal Medicine, of "Alexandra" Hospital, of National and Kapodistrian University of Athens in a study period of 3 years, from December 2019 to December 2022.

Ethics Committee

The research protocol was approved by the Alexandra's Hospital Ethics Committee with written consent obtained from participants. Table 1 displays all patients' characteristics.

Inclusion and exclusion criteria

All patients included in this study met the following criteria: they were between 28 and 40 weeks of gestation, had a singleton pregnancy, and agreed to participate in the study by providing written informed consent. The inclusion criteria for the COVID+ group required a confirmed positive SARS-CoV-2 test via PCR or serological testing. The exclusion criteria were as follows: multiple pregnancies, known fetal pathology, other maternal pathology, hypertension or pre-eclampsia diagnosed during recruitment to the study, and oligamnios were all excluded from the patients selected. All patients had 1st-trimester ultrasound screening for the correct calculation of the gestational age. Patients who met the inclusion criteria and had no exclusion criteria were included in the study. This ensured a homogenous sample with minimized confounding factors. The study ultimately included 38 pregnant women with SARS-CoV-2 (group A) and 43 non-COVID pregnant women (group B).

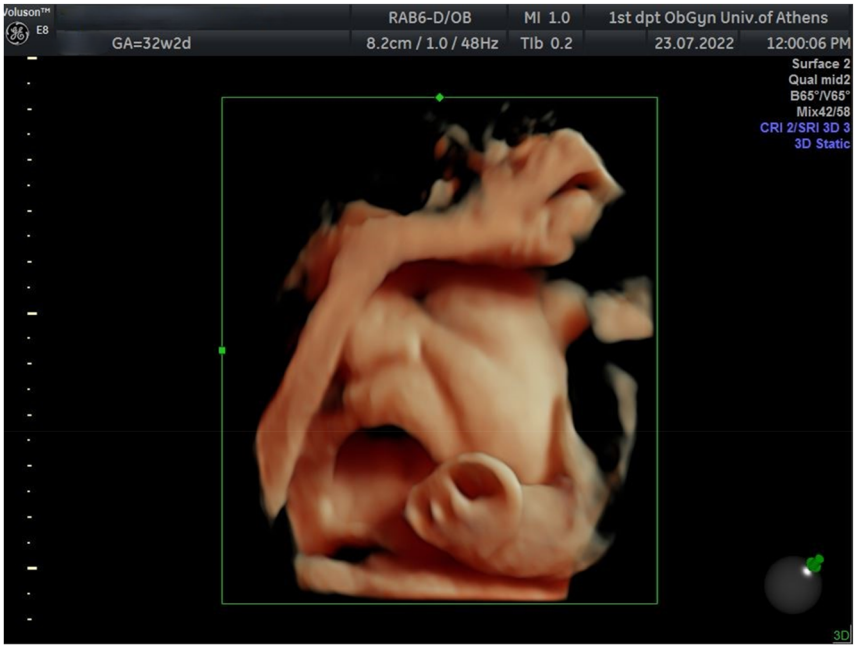

Figure 1: Yawning.

Table 1: Demographic characteristics of pregnant women and adverse pregnancy outcomes.

Characteristics	Group A COVID+ (sample 38)	Group B COVID− (sample 43)	Total patients' mean value or percentage, % Sample=81	Association with abnormal KANET (p-value)
Maternal age, years				> 0.001
Mean value	29.1	33.9	31.5 (17–46)	
Median value			24	
Parity				
Primigravida	15 (39.4 %)	18 (41.8 %)	33 (40.7 %)	
Multigravida	23 (60.6 %)	25 (58.2 %)	48 (59.3 %)	
Nationality				
Caucasian	36 (94.7 %)	36 (83.7 %)	72 (%)	
African American	2 (5.3 %)	7 (16.3 %)	9 (%)	
Smoking				
No	37 (97.3 %)	40 (93 %)	77 (89 %)	
Yes	1 (2.7 %)	3 (7 %)	4 (11 %)	
Week of infection				
Mean value	31 (27–35)			
Median value	33			
Conception				
Normal	38 (100 %)	41 (95.3 %)	79 (96 %)	
ART	0	2 (4.7 %)	2 (4 %)	
BMI, kg/m^2	25.10 (mean)	27.24 (mean)	26.17	
Height, cm/weight, kg			163/66.7	
Previous adverse pregnancy outcome			2 (1.1 %)	
CP	0	0	0 (0 %)	
Metabolic disorder	0	1 (2.3 %)	1 (1.2 %)	
1st trimester bleeding				
Yes	11 (28.9 %)	14 (36.8 %)	25 (30.8 %)	
No	27 (71 %)	29 (63.2 %)	56 (69.2 %)	
Gestational age at delivery				
≥ 37 weeks	32 (84.2 %)	39 (90.7 %)	71 (87.6 %)	
< 37 weeks	6 (15.8 %)	4 (9.3 %)	10 (12.3 %)	
Preeclampsia			3 (3.7 %)	
Group A			2 (5.2 %)	
Group B			1 (2.3 %)	
Gestational diabetes			7 (8.6 %)	
Group A			4 (10.5 %)	
Group B			3 (6.9 %)	
Range of birth weights				
Group A			2,350–3,640	
Group B			2,820–3,450	

KANET, Kurjak's antenatal neurodevelopmental test; BMI, body mass index; CP, cord prolapse; ART, assisted reproductive techniques.

Data collection methods

KANET test was applied to participants twice during the first week of covid infection via abdominal ultrasound using a GE Voluson 730 Pro (GE Healthcare, USA – 4D Wide Band Convex probe). All tests lasted about 20 min and they were performed by the same experienced examiner. According to the Osaka consensus statement, KANET's performance consisted of the following parameters: isolated head/hand/leg movements, cranial sutures, hand to face/head, finger movements, yawning-mouthing, facial expressions, eye blinking, and "Gestalt" perception. 0–5 values are seen as abnormal, 6–13 as borderline, and 14 or above as normal.

Statistical analysis

Statistical package for social sciences (SPSS) was used for data analysis. For all quantitative variables, the mean, median, and measures of dispersion (standard deviation and standard error) were determined. By using Kolmogorov–Smirnov tests, the normality of the data was determined. For properly distributed data, the t-test was used to compare means. For data and scores that were skewed, the Mann–Whitney test was used. Frequencies and proportions were used to define qualitative or category variables. 2-test or Fisher's exact test was used to compare proportions, depending on which was most suitable. All statistical tests had two outcomes. At p 0.05, statistical significance was established.

Results

No statistically significant differences were observed between the two groups regarding the maternal age (33±3.9 years for group A vs. 31±4.1 years for group B) and gestational age (33±1.6 weeks for group A compared to 33±2.1 weeks for group B). Performance of the KANET test varied from 8.30 am to 20.00 pm (Table 2). After analysis of the KANET results of each group, no abnormal scores were identified in both groups, while the borderline scores were both 1 while normal scores were 37 (97.4 %) and 42 (97.7 %) for groups A and B respectively. Further analysis with the KANET score showed small differences between the two groups for isolated eye blinking, facial alterations and finger movements, but no differences in each case scoring were observed (Table 3).

Table 2: KANET study group.

Methods	Numbers, n
Prospective longitudinal cohort study	
Gestational age	28–40 weeks
Singleton pregnancies	(Early dating US)
December 2019–December 2022	3 years
Fetal and Maternal Medicine Unit, "Aexandra" Maternity Hospital, University of Athens	
Study approved by the Ethics Committee/consent form	
Two operators (all reviewed by one)	
Number of participants	81
Number of KANET performed	81
Neonatal follow-up	1–3 days of life
Time of performance of KANET	08.30–20.00 (mean 11.00)
GE Voluson 730 Pro/GE E8	

KANET, Kurjak's antenatal neurodevelopmental test; GE, General Electric.

Table 3: Comparison of KANET scores between the two groups.

Population	Group A (COVID +)	Group B (COVID −)	p-Value
Number of patients	n=38	n=43	
KANET performed	n=38	n=43	Total=81
GA at KANET (weeks)	33±1.6	33±2.1	
N of KANET/patient	1	1	
Total score			
Median	15	16	> 0.001
Range	14–17	15–17	
Interpretation			
Abnormal	0	0	> 0.001
Borderline	1 (2 %)	0	
Normal	37 (98 %)	43 (100 %)	

KANET, Kurjak's antenatal neurodevelopmental test; GA, Gestational Age.

Discussion

The comprehensive effects of COVID-19 on gestational outcomes are yet to be fully discerned, particularly with the ongoing accumulation of new data. Potential alterations in the risk of COVID-19 due to the unique pathophysiological changes of pregnancy remain hypothetical, as there is a lack of robust data to confirm these effects. The infection's presence during any stage of pregnancy may elevate the risk of serious illness, which in turn could lead to considerable complications and noteworthy negative outcomes in particular scenarios. Research has indicated that being infected with SARS-CoV-2 while pregnant could lead to a range of serious complications, including an increased likelihood of preeclampsia, early delivery, gestational diabetes, infants with low birth weights, and stillbirths [15–18]. Additionally, cases of pneumonia caused by SARS-CoV-2 have been connected to a spectrum of adverse outcomes, such as early onset of labor, breaking of waters before labor begins, fetal growth being inhibited, fetal loss, and even neonatal fatalities.

The CDC reports indicate that pregnant individuals are at a twofold increase in risk for ICU admissions, 2.4 times more likely to undergo extracorporeal membrane oxygenation, and have a 1.7 times greater risk of mortality due to severe illness. This group also faces a greater likelihood of hospital admittance and the necessity for oxygen supplementation and invasive ventilation [19–21]. In the U.S., a more severe progression of COVID-19 tends to affect pregnant women who are economically disadvantaged, particularly within the Hispanic community, those without medical insurance, and interestingly, those living in less crowded homes [22, 23].

Findings from the UK corroborate that black individuals, those of advanced maternal age, and those with comorbidities like obesity, respiratory diseases, high blood pressure, and diabetes before pregnancy are subject to increased danger of intense COVID-19 infection and unfavorable outcomes during and after pregnancy [24, 25]. In our investigation, we delve into the assessment of neurodevelopmental trajectories using KANET scores among pregnant women affected by COVID-19 compared to those not affected by the virus, to ascertain the feasibility of predicting deviations in fetal neurodevelopment.

Our analysis did not reveal any notable statistical variance in the score distributions between the cohorts. Moreover, the neurodevelopmental outcomes of newborns appeared unaffected by whether the mothers had contracted COVID-19 during pregnancy. Recent studies have shown varying impacts of maternal COVID-19 on fetal neurodevelopment. For instance, research indicates potential risks associated with low oxygen saturation in severe cases of COVID-19, which could affect fetal neurobehavior [26, 27]. Our findings, however, suggest no significant differences in neurodevelopmental outcomes between the COVID+ and control groups, likely due to the low-risk profile of the included cases. The lack of significant differences in KANET scores between the COVID+ and control groups suggests that SARS-CoV-2 infection during the third trimester may not be associated with altered fetal neurodevelopment. However, the relatively small sample size and the predominance of mild COVID-19 cases may limit the generalizability of these findings. Further studies with larger cohorts and a broader range of COVID-19 severity are necessary to confirm these results.

There are some limitations to be stated considering our study. When SARS-CoV-2 infection was initially detected, our study protocol was designed with the hypothesis of evaluating patients with pneumonia who were at high risk for being infected by this new virus, especially those who had been in Asia or came in contact with Asian tourists in the preceding three months. It was not until February 2020, when the World Health Organization (WHO) officially announced SARS-CoV-2 as a global threat and PCR testing became the gold standard for COVID-19 detection, that we adapted our protocol to specifically focus on COVID-19 during pregnancy.

Additionally, one of the main limitations of our study is the absence of patients with severe COVID-19 symptoms. Our hospital was not responsible for treating pregnant patients with severe COVID-19, and such cases were either transferred to the designated hospital or did not reach our clinic. As a result, all COVID-19 positive cases included in this study were either asymptomatic or presented with mild to moderate symptoms (fever, cough, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting). This limitation has also influenced the sample size and the characteristics of the COVID-19 group in our study. Furthermore, there were no reports of neonatal COVID-19 infection with severe symptoms in our study cohort, a significant factor contributing to the relatively small sample size of 38 pregnancies in the COVID-19 group.

These limitations should be considered when interpreting the findings, as the absence of severe cases means that our results may not be generalizable to all pregnant women with COVID-19, particularly those with severe symptoms.

Conclusions

With the development of 4D ultrasonography, the KANET scoring system [20] has been created. It is the first ultrasound scoring system to measure prenatal neurological behavior for routine screening [21]. Other studies have previously used KANET scoring system in order to evaluate fetal neurological behavior in low- and high-risk gestations. All investigations revealed substantial differences between high- and low-risk groups in prenatal neurological functioning. In addition, abnormal prenatal KANET scores were related with impaired neurobehavioral development [8]. In our study, maternal SARS-CoV-2 was not correlated with aberrant fetal neurological behavior. The research was restricted by the small sample size and the absence of a link between prenatal neurological abnormalities and postnatal neurological outcomes. Future research on a bigger patient sample is required to link prenatal and neonatal data in order to increase our knowledge of the influence of maternal SARS-CoV-2 infection on the neurological health of infants.

Research ethics: The local Institutional Review Board has approved conduction of this study.
Informed consent: Informed consent was obtained from all individuals included in this study, or their legal guardians or wards.
Author contributions: The authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: The authors state no conflict of interest.
Research funding: None declared.
Data availability: Not applicable.

References

1. McMahon CL, Castro J, Silvas J, Muniz Perez A, Estrada M, Carrion R Jr., et al. Fetal brain vulnerability to SARS-CoV-2 infection. Brain Behav Immun 2023;112:188–205.
2. McMahon CL, Hurley EM, Muniz Perez A, Estrada M, Lodge DJ, Hsieh J. Prenatal SARS-CoV-2 infection results in neurodevelopmental and behavioral outcomes in mice. JCI Insight 2024;9:e179068.
3. Dashraath P, Wong JLJ, Lim MXK, Lim LM, Li S, Biswas A, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol 2020;222:521–31.
4. Huntley BJF, Huntley ES, Di Mascio D, Chen T, Berghella V, Chauhan SP. Rates of maternal and perinatal mortality and vertical transmission in pregnancies complicated by severe acute respiratory syndrome coronavirus 2 (SARS-Co-V-2) infection: a systematic review. Obstet Gynecol 2020;136:303–12.
5. Antsaklis P, Antsaklis A. The assessment of fetal neurobehavior with four-dimensional ultrasound: the Kurjak antenatal neurodevelopmental test. Donald Sch J Ultrasound Obstet Gynecol 2012;6:362–75.
6. Kurjak A, Tikvica A, Stanojevic M, Miskovic B, Ahmed B, Azumendi G, et al. The assessment of fetal neurobehavior by three-dimensional and four-dimensional ultrasound. J Matern Fetal Neonatal Med 2008;21:675–84.
7. Amiel-Tison C, Gosselin J, Kurjak A. Neurosonography in the second half of fetal life: a neonatologist's point of view. J Perinat Med 2006;34:437–46.
8. Kurjak A, Talic A, Honemeyer U, Stanojevic M, Zalud I. Comparison between antenatal neurodevelopmental test and fetal Doppler in the assessment of fetal well being. J Perinat Med 2013;41:107–14.
9. Greenwood C, Newman S, Impey L, Johnson A. Cerebral palsy and clinical negligence litigation: a cohort study. BJOG 2003;110:6–11.
10. Strijbis EM, Oudman I, van Essen P, MacLennan AH. Cerebral palsy and the application of the international criteria for acute intrapartum hypoxia. Obstet Gynecol 2006;107:1357–65.
11. de Vries JI, Fong BF. Changes in fetal motility as a result of congenital disorders: an overview. Ultrasound Obstet Gynecol 2007;29:590–9.
12. de Vries JI, Visser GH, Prechtl HF. The emergence of fetal behaviour. II. Quantitative aspects. Early Hum Dev 1985;12:99–120.
13. Edelberg SC, Dierker L, Kalhan S, Rosen MG. Decreased fetal movements with sustained maternal hyperglycemia using the glucose clamp technique. Am J Obstet Gynecol 1987;156:1101–5.
14. Cosmi EV, Anceschi MM, Cosmi E, Piazze JJ, La Torre R. Ultrasonographic patterns of fetal breathing movements in normal pregnancy. Int J Gynaecol Obstet 2003;80:285–90.
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 (Can Med Assoc J) 2021;193:E540–8.
16. Villar J, Ariff S, Gunier RB, Thiruvengadam R, Rauch S, Kholin A, et al. Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: the INTERCOVID multinational cohort study. JAMA Pediatr 2021;175:817–26.
17. DeSisto CL, Wallace B, Simeone RM, Polen K, Ko JY, Meaney-Delman D, et al. Risk for stillbirth among women with and without COVID-19 at delivery hospitalization – United States, March 2020–September 2021. MMWR Morb Mortal Wkly Rep 2021;70:1640–5.
18. Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al. 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. MMWR Morb Mortal Wkly Rep 2020;69:1641–7.
19. Badr DA, Mattern J, Carlin A, Cordier AG, Maillart E, El Hachem L, et al. Are clinical outcomes worse for pregnant women at ≥20 weeks' gestation infected with coronavirus disease 2019? A multicenter case-control study with propensity score matching. Am J Obstet Gynecol 2020;223:764–8.
20. Lokken EM, Huebner EM, Taylor GG, Hendrickson S, Vanderhoeven J, Kachikis A, et al. Disease severity, pregnancy outcomes, and maternal deaths among pregnant patients with severe acute respiratory syndrome coronavirus 2 infection in Washington State. Am J Obstet Gynecol 2021;225:77.e1–14.
21. Emeruwa UN, Ona S, Shaman JL, Turitz A, Wright JD, Gyamfi-Bannerman C, et al. Associations between built environment, neighborhood socioeconomic status, and SARSCoV-2 infection among pregnant women in New York City. JAMA 2020;324:390–2.
22. Joseph NT, Stanhope KK, Badell ML, Horton JP, Boulet SL, Jamieson DJ. Sociodemographic predictors of SARS-CoV-2 infection in obstetric patients, Georgia, USA. Emerg Infect Dis 2020;26:2787–9.
23. Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population-based cohort study. BMJ 2020;369:2107.
24. Galang RR, Newton SM, Woodworth KR, Griffin I, Oduyebo T, Sancken CL, et al. Risk factors for illness severity among pregnant women with confirmed SARS-CoV-2 infection – surveillance for emerging threats to mothers and babies network, 22 state, local, and territorial health departments, March 29, 2020–March 5, 2021. Clin Infect Dis 2021;73:S17–23.
25. World Health Organization. Definition and categorization of the timing of mother-to-child transmission of SARS-CoV-2 scientific brief; 2021. https://apps.who.int/iris/handle/10665/339422 [Accessed 20 Jul 2022].
26. Pecks U, Mand N, Kolben T, Rüdiger M, Oppelt P, Zöllkau J, et al. The CRONOS Registry. SARS-CoV-2 infection during pregnancy. Dtsch Arztebl Int 2022;119:588–94.
27. Günther J, Ziert Y, Andresen K, Pecks U, von Versen-Höynck F, Ajouby S, et al. Variability in COVID-19 symptom presentation during pregnancy and its impact on maternal and infant outcomes across the pandemic. Int J Infect Dis 2024;146:107157.