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Clinical factors in SARS-CoV-2 antibody response in unvaccinated mothers

<https://doi.org/10.1515/jpm-2025-0349>

Received June 28, 2025; accepted October 5, 2025;

published online November 17, 2025

Abstract

Objectives: Understanding the clinical factors influencing the SARS-CoV-2 antibody response during and after pregnancy is critical for optimizing maternal care and vaccination strategies. This prospective cohort study aimed to evaluate associations between maternal clinical characteristics and SARS-CoV-2-specific IgG and IgA antibody levels at delivery and 42 days postpartum in unvaccinated pregnant women.

Methods: A total of 387 pregnant women with confirmed SARS-CoV-2 infection during pregnancy were included. SARS-CoV-2 infection was confirmed using real-time RT-PCR. Clinical data, including age, body mass index (BMI), smoking status, pre-existing morbidities, and obstetric complications, were recorded. SARS-CoV-2-specific IgG and IgA antibodies were quantified using ELISA at delivery and 42 days postpartum.

Results: Higher preconception BMI significantly correlated with increased odds of detecting IgG and IgA antibodies at both delivery and postpartum assessments ($p < 0.05$),

independently of maternal age and chronic diseases. Women without chronic systemic diseases exhibited lower antibody levels at delivery, whereas smokers had significantly lower odds of IgG antibody presence at delivery. Additionally, pre-existing cardiovascular diseases were associated with reduced antibody presence at six weeks postpartum. Other clinical parameters did not show significant associations.

Conclusions: Preconception BMI and pre-existing systemic diseases may modulate SARS-CoV-2 antibody responses in pregnant women. These clinical factors should inform assessments of maternal and neonatal infection risks and guide vaccination strategies in pregnant populations. Further research is needed to elucidate the mechanisms underlying these associations.

Keywords: SARS-CoV-2; IgG and IgA antibodies; pregnancy; body mass index; comorbidity; postpartum period

Introduction

Despite the emergence of less virulent SARS-CoV-2 variants and increased population-level immunity through vaccination and prior exposure, concerns remain regarding the virus's impact on vulnerable groups, particularly pregnant women. Although most SARS-CoV-2 infections during pregnancy are asymptomatic or mild [1], accumulating evidence indicates a higher risk for severe COVID-19 and adverse obstetric outcomes in this population. Compared to non-pregnant individuals, pregnant women exhibit greater susceptibility to complications such as severe pneumonia, ICU admission, oxygen therapy, mechanical ventilation, and extracorporeal membrane oxygenation. Furthermore, infection during pregnancy has been associated with elevated risks of premature rupture of membranes, impaired fetal perfusion, and preterm birth [2–4].

Pregnancy induces physiological adaptations – including increased cardiovascular demand, reduced pulmonary capacity, and immunological shifts – that may exacerbate SARS-CoV-2 severity and complications [5]. Although not necessarily immunosuppressive, pregnancy reprioritizes immunity by enhancing innate defenses and downregulating adaptive inflammatory responses, particularly in later stages [6]. Understanding SARS-CoV-2 immune dynamics across pregnancy

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and postpartum is essential for optimizing clinical care, informing vaccination strategies, and preparing for future infectious threats in this population.

Emerging evidence suggests that demographic and clinical factors influence COVID-19 severity in pregnancy [2, 7]. A living systematic review of over 400 studies identified increasing maternal age, elevated body mass index (BMI), non-white ethnicity, pre-existing hypertension or diabetes, and pregnancy-specific conditions such as gestational diabetes and preeclampsia as risk factors for severe outcomes [2]. Although SARS-CoV-2 infection elicits dynamic immune and cytokine responses during and after pregnancy [8], associations between maternal clinical or lifestyle characteristics and antibody responses remain poorly defined. Identifying factors linked to a robust antibody response could improve risk stratification, guide clinical decisions, and inform vaccine strategies in pregnant populations. Moreover, because pregnant and lactating women were excluded from initial COVID-19 vaccine and treatment trials [9], targeted research on pregnancy-specific immune responses is essential to adapt findings from the general population to this unique group.

This study investigated the associations between maternal clinical characteristics and SARS-CoV-2 IgG and IgA antibody responses at delivery and six weeks postpartum. We analyzed a unique cohort of unvaccinated women infected before the emergence of the Delta variant, allowing for an examination of the natural immune response without confounding from vaccination or subsequent viral evolution.

Subjects and methods

Study design and ethical considerations

This prospective study was conducted at a tertiary perinatal care center in collaboration with a microbiology and immunology laboratory. Data were collected from September 2020 to March 2021, prior to circulation of the SARS-CoV-2 Delta variant and before the initiation of COVID-19 vaccination programmes. Participation was voluntary, with written informed consent obtained from all participants. The study was approved by the Medical Ethics Committee of the Republic of Slovenia (permit no. 0120–196/2020-18) and conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Participants and study variables

This prospective cohort study included 387 pregnant women with SARS-CoV-2 infection confirmed by reverse-transcription

polymerase chain reaction (RT-PCR) on nasopharyngeal swabs. The primary outcome was the presence of SARS-CoV-2-specific IgG and IgA antibodies, measured by ELISA in venous blood samples collected at delivery (n=387) and 42 days postpartum (n=286). Independent variables included maternal clinical characteristics, SARS-CoV-2 disease course, pre-existing comorbidities, and obstetric factors assessed during pregnancy, delivery, and postpartum.

COVID-19 was classified as asymptomatic or symptomatic based on the presence of symptoms at the time of a positive SARS-CoV-2 test. Symptomatic infection included any of the following: fever, cough, malaise, dyspnea, myalgia, sore throat, anosmia, ageusia, gastrointestinal symptoms, or diarrhea. Severe disease was defined by ≥ 30 breaths/min, $SpO_2 < 94\%$ on room air, $PaO_2/FiO_2 < 300$ mmHg, or $> 50\%$ lung infiltrates on imaging [10].

Clinical and demographic data were collected during pregnancy, at delivery, and during postpartum visits. Demographic variables included maternal age (years), gestational age at delivery (weeks), BMI (calculated in kilograms per square metre), and smoking status (yes/no). Chronic comorbidities were assessed and included respiratory diseases (e.g. asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, pneumonitis), thyroid disorders (e.g. hypothyroidism, hyperthyroidism, goitre, thyroid tumours), and autoimmune diseases (e.g. rheumatoid arthritis, scleroderma, systemic lupus erythematosus, Sjögren's syndrome). Gastrointestinal disorders included irritable bowel syndrome, Crohn's disease, inflammatory bowel disease, lactose intolerance, and gastroesophageal reflux disease. Hypertension was defined as systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg. Neurological conditions included epilepsy, tumours, multiple sclerosis, and myasthenia gravis. Other comorbidities included diabetes mellitus (type 1 or type 2), cardiovascular disease (e.g. endocarditis, conduction disorders), thromboembolic events (deep vein thrombosis, pulmonary embolism), renal disease (e.g. chronic kidney disease, recurrent urinary tract infections), malignancy, and psychiatric disorders (e.g. anxiety, depression, post-traumatic stress disorder).

Obstetric characteristics were categorised as gestational (occurring during pregnancy), peripartum (at the time of delivery), or postpartum. Gestational conditions included gestational hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic ≥ 90 mmHg after 20 weeks in a previously normotensive woman) [11], preeclampsia (hypertension with proteinuria or any other organ involvement after 20 weeks), eclampsia (preeclampsia with seizures) [12], and HELLP syndrome (haemolysis, elevated liver enzymes, and low platelet count) [13]. Intrauterine growth restriction was defined as

estimated fetal weight or abdominal circumference below the 10th percentile for gestational age. Other conditions included gestational diabetes, deep vein thrombosis, pulmonary embolism, anaemia (haemoglobin <110 g/L in the first trimester, <105 g/L in the second and third trimesters, <100 g/L postpartum) [14], and hepatic disorders such as intrahepatic cholestasis of pregnancy (elevated bile acids or pruritus with transaminase elevation) [15] and hepatopathy (elevated liver enzymes). Antepartum haemorrhage was also recorded. Peripartum characteristics included mode of delivery, operative vaginal delivery, non-progressive labour (per American College of Obstetricians and Gynecologists criteria), fetal distress, abnormal presentation, placental abruption, and prior uterine surgery. Postpartum characteristics included postpartum haemorrhage (blood loss >500 mL).

SARS-CoV-2 testing and antibody detection

Details of the laboratory procedures have been previously described [16]. Briefly, SARS-CoV-2 ribonucleic acid (RNA) was detected from nasopharyngeal swabs using real-time reverse transcription polymerase chain reaction (RT-PCR) on the Cobas 6,800 platform (Roche Diagnostics, Alameda, CA, USA). The assay targeted two viral sequences: ORF1 and the envelope protein E gene. Amplification of both targets indicated a positive result. An internal control RNA confirmed successful extraction and amplification.

To assess the humoral immune response, SARS-CoV-2-specific immunoglobulin G (IgG) and immunoglobulin A (IgA) antibodies were measured in serum using Euroimmun Anti-SARS-CoV-2 ELISA IgG and IgA kits (Euroimmun, Medizinische Labordiagnostika AG, Lübeck, Germany) at the Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana. The assay is based on an indirect enzyme-linked immunosorbent assay (ELISA) in which viral antigens are immobilised on a microtiter plate. Antibody concentration was calculated as the ratio of sample absorbance to the calibrator. A ratio ≥ 0.8 was considered positive, and < 0.8 negative.

Statistical analysis

All analyses were conducted using IBM SPSS Statistics for Windows, version 28.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were reported as frequencies and proportions. Normally distributed variables were presented as mean and standard deviation, and non-normally distributed variables as median and interquartile range (IQR). Normality was assessed using the Shapiro–Wilk test.

Associations between maternal clinical characteristics and antibody presence were evaluated using univariate and multivariable logistic regression. Multiple linear regression was applied to assess relationships with antibody levels. Spearman's rank correlation coefficient was used to assess the association between IgG and IgA levels. A p-value < 0.05 was considered statistically significant.

Results

Clinical and obstetric characteristics of the participants

The analysis included 387 unvaccinated women who were positive for SARS-CoV-2 antibodies at delivery. Although cohort details have been previously reported [16], key clinical and obstetric characteristics are summarised for context (Table 1). The median maternal age was 31 years (interquartile range, 28–34 years). Median preconception BMI was 23.9 kg/m² (IQR, 21.4–26.9), and at delivery, 28.7 kg/m² (IQR, 26.0–32.2). Most participants (70.2 %, 271/386) reported no pre-existing chronic systemic disease, while 30.2 % (117/387) had at least one chronic comorbidity. Current smoking was reported in 7.3 % (28/385). Minor discrepancies in denominators reflect missing data.

About half of participants tested positive for SARS-CoV-2 at or before 31 4/7 weeks of gestation (IQR: 20 0/7–37 5/7). Asymptomatic infection occurred in 11.9 % (46/387); the remainder reported symptoms. The most frequent were altered smell (57.7 %, 222/386), cough (45.2 %, 174/385), fatigue (44.4 %, 171/385), and malaise (43.1 %, 166/385). Severe COVID-19 was reported in 1.3 % (5/385).

Pregnancy complications occurred in 42.1 % (163/387), with gestational diabetes in 20.7 % (80/387) and anaemia in 33.9 % (131/387). Median gestational age at delivery was 39 2/7 weeks (IQR: 38 3/7–40 0/7). Most women delivered vaginally (69.8 %, 270/387). Need for emergency caesarean section was the most common peripartum complication (12.4 %, 48/387). Postpartum complications were observed in 11.9 % (46/387), most frequently postpartum haemorrhage >500 mL (9.0 %, 35/387).

Maternal clinical characteristics and IgG/IgA antibody profile at delivery

At delivery, IgG antibodies were detected in 45.7 % (177/387) and IgA antibodies in 58.9 % (228/387) of participants, as previously reported [16]. All women with severe COVID-19 had detectable antibodies. Table 2 presents univariate

associations between maternal characteristics and antibody presence. For IgG, significant associations were observed

Table 1: Maternal clinical and obstetric characteristics during pregnancy, delivery and postpartum.

General clinical and obstetric characteristics	
Age, years (Me (IQR))	31 (28–34)
Height, cm (M (SD))	166.9 (5.7)
Pre-pregnancy body weight, kg (Me (IQR))	66 (59–75)
BMI preconception, kg/m ² (Me (IQR))	23.9 (21.4–26.9)
Smoking (n=358)	26 (7.3)
BMI at birth, (n=348), kg/m ² (Me (IQR))	28.7 (26–32.2)
Gestational age at delivery, weeks/days (Me (IQR))	39 2/7 (38 3/7–40 0/7)
Vaginal birth	270 (69.8)
Medical and obstetric disorders	
Chronic diseases	117 (30.2)
Thyroid disorder	23 (5.9)
Autoimmune disorder	18 (4.7)
Cardiovascular diseases	14 (3.6)
Gastrointestinal diseases	12 (3.1)
Hypertension	10 (2.6)
Neurological disorders	10 (2.6)
Diabetes	6 (1.6)
Carcinoma	4 (1)
Psychiatric disorders	3 (0.8)
Renal diseases	3 (0.8)
Thrombembolic complications	1 (0.3)
Gestational	
Complications of pregnancy	163 (42.1)
Anaemia	131 (33.9)
Gestational diabetes	80 (20.7)
IUGR	36 (9.3)
Hepatopathy	12 (3.1)
Gestational hypertension	9 (2.3)
Pre-eclampsia	7 (1.8)
Bleeding	4 (1)
DVT/PE	2 (0.5)
Eclampsia (n=385)	0 (0)
HELLP	0 (0)
Perinatal/Postnatal	
Planned caesarean section	49 (12.7)
Urgent caesarean section	48 (12.4)
Operative vaginal birth	10 (2.6)
Foetal distress	23 (5.9)
Non-progressive labour	17 (4.4)
Placental abruption	3 (0.8)
Obstructed labour	8 (2.1)
Previous CS or myomectomy	38 (9.8)
Postpartum haemorrhage over 500 mL	35 (9)

Normally distributed numeric variables are presented as mean (M) and standard deviation (SD), and other variables as median (Me) and interquartile range (IQR); n=387, except otherwise indicated. BMI, body mass index; CS, cesarean section; DVT, deep vein thrombosis; HELLP, hemolysis, elevated liver enzymes and low platelets; IUGR, intrauterine growth restriction; PE, pulmonary embolism; SD, standard deviation.

with preconception BMI ($p=0.014$) and smoking status ($p=0.037$). Each unit increase in BMI was associated with 5 % higher odds of IgG detection (odds ratio [OR] = 1.05; 95 % confidence interval [CI]: 1.01–1.10). Smokers had lower odds of IgG detection than non-smokers (OR=0.39; 95 % CI: 0.16–0.94). Other maternal variables, including age and overall health status, were not significantly associated with IgG presence in univariate models. IgA antibody presence was also significantly associated with preconception BMI ($p=0.012$); each unit increase in BMI increased the odds of IgA detection by 6 % (OR=1.06; 95 % CI: 1.01–1.11).

In multivariable logistic models adjusting for maternal age, BMI, and chronic disease status, BMI remained significantly associated with both IgG (OR=1.05; 95 % CI: 1.00–1.09) and IgA (OR=1.05; 95 % CI: 1.01–1.10) presence at delivery (Table 3).

Additionally, absence of chronic disease was associated with lower antibody levels in adjusted linear regression models. Women without chronic conditions had 22 % lower IgG ($p=0.038$) and 25 % lower IgA ($p=0.032$) levels at delivery compared to those with chronic disease (Table 4).

Maternal clinical characteristics and IgG/IgA antibody profile at 42 days postpartum

At 42 days postpartum, IgG and IgA antibodies were detected in 72.7 % (208/286) and 74.8 % (214/286) of participants, respectively, as previously described [16]. Table 5 presents associations between clinical characteristics and antibody presence. Presence of IgG antibodies was significantly associated with preconception BMI ($p=0.010$) and showed a borderline association with cardiovascular disease ($p=0.050$). Each unit increase in BMI increased the odds of IgG detection (OR=1.09; 95 % CI: 1.02–1.16), while other cardiovascular diseases was associated with reduced odds (OR=0.30; 95 % CI: 0.09–1.00). No other clinical variables showed significant associations with IgG presence. IgA presence at 42 days postpartum was significantly associated with preconception BMI ($p=0.007$), hypertension ($p=0.030$), cardiovascular disease ($p=0.032$), and IgA presence at delivery ($p<0.001$). Elevated BMI increased odds of IgA detection (OR=1.10; 95 % CI: 1.03–1.17). All women with hypertension had detectable IgA, while other cardiovascular diseases was associated with lower odds (OR=0.26; 95 % CI: 0.08–0.89). After adjusting for maternal age, BMI, and chronic disease status, no associations remained significant (Table 3). In the linear model (Table 4), chronic disease was associated with 22 % higher IgG levels, and each year of maternal age corresponded to a 2 % increase. No adjusted associations were observed for IgA levels.

Table 2: Associations between maternal clinical characteristics and the presence of IgG and IgA antibodies in the maternal blood at delivery.

Characteristics	IgG antibodies				IgA antibodies			
	IgG NO (n=210)	IgG YES (n=177)	OR (95 % CI)	p-Value	IgA NO (n=159)	IgA YES (n=228)	OR (95 % CI)	p-Value
Age, years, Me (IQR)	30 (27–34)	31 (28–34)	1.01 (0.97–1.06)	0.606	31 (27–34)	31 (28–34)	1.01 (0.97–1.06)	0.565
Preconception BMI, kg/m ² , Me (IQR)	23.5 (21–26.4)	24.2 (21.9–27.5)	1.05 (1.01–1.1)	0.014	23.8 (21.1–25.4)	24.1 (21.6–27.9)	1.06 (1.01–1.11)	0.012
Smoking ^b	19 (10.1)	7 (4.1)	0.39 (0.16–0.94)	0.037	12 (8.5)	14 (6.5)	0.74 (0.33–1.65)	0.465
Maternal health status								
Healthy	153 (73.2)	118 (66.7)	0.73 (0.47–1.13)	0.162	111 (70.3)	160 (70.2)	1 (0.64–1.55)	0.987
Chronic diseases	58 (27.6)	59 (33.3)	1.31 (0.85–2.02)	0.223	49 (30.8)	68 (29.8)	0.95 (0.61–1.48)	0.834
Thyroid disease	10 (4.8)	13 (7.3)	1.59 (0.68–3.71)	0.288	9 (5.7)	14 (6.1)	1.09 (0.46–2.58)	0.844
Hypertension	5 (2.4)	5 (2.8)	1.19 (0.34–4.19)	0.784	3 (1.9)	7 (3.1)	1.65 (0.42–6.47)	0.475
Type 1 or 2 diabetes	4 (1.9)	2 (1.1)	0.59 (0.11–3.25)	0.543	2 (1.3)	4 (1.8)	1.4 (0.25–7.75)	0.699
Autoimmune disorder	10 (4.8)	8 (4.5)	0.95 (0.37–2.45)	0.910	10 (6.3)	8 (3.5)	0.54 (0.21–1.4)	0.207
Chronic lung disease	13 (6.2)	14 (7.9)	1.3 (0.59–2.85)	0.509	10 (6.3)	17 (7.5)	1.2 (0.53–2.7)	0.658
Neurological disorders	3 (1.4)	7 (4)	2.84 (0.72–11.15)	0.135	2 (1.3)	8 (3.5)	2.85 (0.6–13.62)	0.188
Gastrointestinal diseases	4 (1.9)	8 (4.5)	2.44 (0.72–8.24)	0.151	4 (2.5)	8 (3.5)	1.41 (0.42–4.76)	0.581
Psychiatric disorders	2 (1)	1 (0.6)	0.59 (0.05–6.57)	0.669	1 (0.6)	2 (0.9)	1.4 (0.13–15.55)	0.785
Carcinoma	1 (0.5)	3 (1.7)	3.6 (0.37–34.95)	0.269	2 (1.3)	2 (0.9)	0.69 (0.1–4.98)	0.717
Cardiovascular diseases	9 (4.3)	5 (2.8)	0.65 (0.21–1.97)	0.446	8 (5)	6 (2.6)	0.51 (0.17–1.5)	0.221
Thromboembolic complications	0 (0)	1 (0.6)		0.303 ^a	0 (0)	1 (0.4)		0.303 ^a
Renal diseases	2 (1)	1 (0.6)	0.59 (0.05–6.57)	0.669	2 (1.3)	1 (0.4)	0.35 (0.03–3.85)	0.388

Normally distributed numeric variables are presented as mean (M) and standard deviation (SD), and other variables as median (Me) and interquartile range (IQR); n=387, except otherwise indicated. BMI, body mass index; CI, confidence interval; IgG, immunoglobulin G; IgA, immunoglobulin A; OR, odds ratio; p significant at <0.05. ^aA likelihood ratio test. ^b(Smoking) IgG NO n=189, IgG YES n=169; IgA NO n=141; IgA YES n=217.

Table 3: Association of maternal age, preconception BMI, and health status with IgG and IgA antibody presence at delivery and 42 days postpartum.

	Multiple logistic regression ^a							
	IgG at delivery		IgA at delivery		IgG 42 days postpartum		IgA 42 days postpartum	
	aOR (95 % CI)	p-Value	aOR (95 % CI)	p-Value	aOR (95 % CI)	p-Value	aOR (95 % CI)	p-Value
Age	1 (0.96–1.05)	0.971	1 (0.96–1.05)	0.862	0.96 (0.89–1.04)	0.308	0.97 (0.9–1.04)	0.371
Preconception BMI	1.05 (1–1.09)	0.03	1.05 (1.01–1.1)	0.025	1.04 (0.97–1.13)	0.258	1.06 (0.98–1.14)	0.159
Healthy	0.8 (0.51–1.26)	0.33	1.12 (0.71–1.78)	0.628	1.42 (0.71–2.87)	0.322	0.85 (0.43–1.69)	0.644

BMI, body mass index; CI, confidence interval; SE, standard error; IgG, immunoglobulin G; IgA, immunoglobulin A; aOR, adjusted odds ratio; p significant at <0.05; ^aThe model only includes subjects with antibodies present at delivery and 42 days postpartum.

Discussion

This prospective cohort study examined associations between maternal clinical characteristics and SARS-CoV-2-specific IgG and IgA antibody responses at delivery and 42 days postpartum in unvaccinated pregnant women.

Higher preconception BMI was significantly associated with greater odds of detecting both IgG and IgA antibodies at both time points, and this relationship persisted after adjustment for maternal age and chronic disease status. Additionally, women without existing comorbidities exhibited lower IgG and IgA levels at delivery, while smokers had reduced odds

Table 4: Association between maternal age, BMI, health status and the presence and level of IgG and IgA antibodies in the blood at delivery and 42 days postpartum.

	Multiple linear regression ^a							
	ln (IgG delivery)		ln (IgA delivery)		ln (IgG 42 days)		ln (IgA 42 days)	
	B (SE)	p-Value	B (SE)	p-Value	B (SE)	p-Value	B (SE)	p-Value
Age	-0.002 (0.011)	0.858	-0.001 (0.012)	0.92	0.02 (0.01)	0.044	-0.008 (0.01)	0.439
Preconception BMI	-0.001 (0.009)	0.928	-0.002 (0.01)	0.808	0.008 (0.008)	0.365	-0.005 (0.009)	0.601
Healthy	-0.221 (0.106)	0.038	-0.259 (0.119)	0.032	-0.22 (0.102)	0.033	-0.203 (0.103)	0.051
R ²	0.06		0.07		0.20		0.19	

B, regression coefficient; BMI, body mass index; CI, confidence interval; SE, standard error; IgG, immunoglobulin G; IgA, immunoglobulin A; OR, odds ratio; p significant at <0.05; ^aThe model only includes subjects with antibodies present at delivery and 42 days postpartum.

Table 5: Associations between maternal clinical characteristics and the presence of IgG and IgA antibodies in the maternal blood at 42 days postpartum.

Characteristics	IgG antibodies				IgA antibodies			
	IgG NO< (n=78)	IgG YES (n=208)	OR (95 % CI)	p-Value	IgA NO (n=72)	IgA YES (n=214)	OR (95 % CI)	p-Value
Age, years	31.5 (29–34)	31 (28–34)	0.95 (0.9–1.01)	0.11	31 (29–34)	31 (28–34)	0.97 (0.91–1.03)	0.275
Preconception BMI, kg/m ²	23 (20.8–26.6)	24.1 (21.5–27.5)	1.09 (1.02–1.16)	0.01	23.2 (20.8–25.4)	24 (21.5–27.5)	1.1 (1.03–1.17)	0.007
Smoking ^b	6 (8.3)	10 (5.2)	0.6 (0.21–1.73)	0.35	4 (6.3)	12 (6)	0.94 (0.29–3.01)	0.912
Maternal health status								
Healthy	52 (66.7)	145 (70)	1.17 (0.67–2.04)	0.58	49 (69)	148 (69.2)	1.01 (0.56–1.8)	0.982
Chronic diseases	27 (34.6)	63 (30.3)	0.82 (0.47–1.43)	0.48	24 (33.3)	66 (30.8)	0.89 (0.5–1.58)	0.694
Thyroid disease	5 (6.4)	14 (6.7)	1.05 (0.37–3.03)	0.92	6 (8.3)	13 (6.1)	0.71 (0.26–1.95)	0.507
Hypertension	1 (1.3)	7 (3.4)	2.68 (0.32–22.16)	0.36	0 (0)	8 (3.7)		0.03 ^a
Type 1 or 2 diabetes	0 (0)	4 (1.9)		0.109 ^a	0 (0)	4 (1.9)		0.126 ^a
Autoimmune disorder	7 (9)	8 (3.8)	0.41 (0.14–1.16)	0.09	5 (6.9)	10 (4.7)	0.66 (0.22–1.99)	0.457
Chronic lung disease	5 (6.4)	13 (6.3)	0.97 (0.34–2.83)	0.96	4 (5.6)	14 (6.5)	1.19 (0.38–3.74)	0.766
Neurological disorders	2 (2.6)	6 (2.9)	1.13 (0.22–5.71)	0.88	1 (1.4)	7 (3.3)	2.4 (0.29–19.85)	0.416
Gastrointestinal diseases	3 (3.8)	6 (2.9)	0.74 (0.18–3.04)	0.68	2 (2.8)	7 (3.3)	1.18 (0.24–5.83)	0.836
Psychiatric disorders	1 (1.3)	1 (0.5)	0.37 (0.02–6.02)	0.49	1 (1.4)	1 (0.5)	0.33 (0.02–5.4)	0.439
Carcinoma	0 (0)	3 (1.4)		0.166 ^a	1 (1.4)	2 (0.9)	0.67 (0.06–7.5)	0.745
Connective tissue disorders	2 (2.6)	4 (1.9)	0.75 (0.13–4.15)	0.74	2 (2.8)	4 (1.9)	0.67 (0.12–3.72)	0.644
Cardiovascular diseases	6 (7.7)	5 (2.4)	0.3 (0.09–1)	0.05	6 (8.3)	5 (2.3)	0.26 (0.08–0.89)	0.032
Thromboembolic complications	0 (0)	1 (0.5)		0.424 ^a	0 (0)	1 (0.5)		0.446 ^a
Renal diseases	0 (0)	3 (1.4)		0.166 ^a	0 (0)	3 (1.4)		0.186 ^a
IgG at delivery	4 (5.1)	116 (55.8)	23.33 (8.22–66.17)	< 0.001				
IgA at delivery					12 (6.7)	151 (70.6)	11.98 (6.04–23.8)	< 0.001

Normally distributed numeric variables are presented as mean (M) and standard deviation (SD), and other variables as median (Me) and interquartile range (IQR); n=387, except otherwise indicated. BMI, body mass index; CI, confidence interval; IgG, immunoglobulin G; IgA, immunoglobulin A; OR, odds ratio; p significant at <0.05. ^aA likelihood ratio test. ^b(Smoking) IgG NO n=72; YES n=192; IgA NO n=63; YES n=201.

of IgG detection. At six weeks postpartum, pre-existing cardiovascular disease was linked to reduced IgG and IgA antibody presence, whereas women without existing comorbidities continued to show lower IgG levels compared to those with chronic conditions. No other maternal or obstetric variables were significantly associated with the antibody profile. These findings highlight the potential

influence of preconception BMI and chronic disease status on the maternal humoral immune response and may inform targeted vaccination and clinical risk assessment strategies in pregnancy and early postpartum period.

The observed association between preconception BMI and both IgG and IgA antibody presence at delivery and 42 days postpartum contributes to the growing

understanding of how adiposity influences immune responses to SARS-CoV-2 in pregnancy. Overweight and obesity are established risk factors for severe SARS-CoV-2 infection, with increased risk evident even at modest BMI elevations [17, 18]. Unlike other viral infections such as influenza, where obesity is associated with diminished seroconversion [19], our findings suggest that higher BMI predicts stronger antibody responses. This likely reflects more severe infection, as elevated SARS-CoV-2 antibody titres have been linked to greater disease severity [20, 21]. Consistent with this, we previously reported that the presence of IgG and IgA antibodies at delivery in this cohort was significantly associated with symptomatic infection during pregnancy [16].

Differences in serological response to SARS-CoV-2 may exist between individuals with higher BMI and those with normal weight, with BMI potentially exerting distinct effects on antibody profiles following natural infection vs. vaccination. For example, while influenza vaccination elicits similar early antibody titres in adults regardless of BMI, titres decline more rapidly in those with obesity over time [22]. In contrast to our findings, a study of 130 pregnant women vaccinated with an mRNA COVID-19 vaccine during the second trimester found no association between maternal IgG levels and BMI or comorbidities [23]. Similarly, Tsatsaris et al. reported no relationship between BMI and IgG response at delivery [24]. However, other studies have shown that higher BMI is linked to faster waning of vaccine-induced antibodies [25], and a recent meta-analysis confirmed lower antibody titres post-vaccination in individuals with obesity [26]. Moreover, SARS-CoV-2 antibodies in obese individuals often exhibit autoimmune rather than neutralising characteristics [27], underscoring the need for studies assessing not only antibody levels but also their protective quality in pregnancy and postpartum.

The association between higher preconception BMI and enhanced SARS-CoV-2 antibody responses may be partly explained by the broader immunological effects of obesity. Elevated BMI in pregnant women has been linked to increased rates of chronic inflammation, maternal and fetal vascular malperfusion, and placental fibrinoid deposition in the setting of SARS-CoV-2 infection [28]. Obesity promotes systemic inflammation through elevated pro-inflammatory cytokines and adipokines – including tumour necrosis factor- α , interleukin (IL)-6, IL-1 β , leptin, and resistin – and activation of immune effector cells [29]. Higher pre-gravid BMI is associated with increased IL-6 and altered levels of granulocyte-macrophage colony-stimulating factor and fibroblast growth factor 2 during pregnancy [30]. Adipose tissue, particularly visceral fat, serves as a major source of IL-6, which may exacerbate cytokine-driven immune responses and has been associated with severe COVID-19

outcomes [31, 32]. Perez de Heredia et al. identified four obesity-related mechanisms of immune dysregulation: altered adipokine profiles, fatty acid-induced inflammation, endoplasmic reticulum stress, and hypoxia-induced immune activation in hypertrophic fat [33]. This pro-inflammatory state may contribute to the heightened antibody response observed in women with elevated preconception BMI [34, 35].

Our findings also suggest a role for pre-existing comorbidities in modulating the maternal antibody response to SARS-CoV-2. Hypertension, cardiovascular disease, and diabetes – common comorbidities in COVID-19 – are closely linked to age-related inflammation and metabolic dysfunction [36, 37]. Women without existing comorbidities had lower IgG and IgA levels at delivery, possibly reflecting milder disease severity and a correspondingly less intense antibody response. Chronic conditions may influence immune responses through dysregulation of both innate and adaptive immunity [37], contributing to severity- and comorbidity-specific immune profiles observed in COVID-19 patients [38]. Interestingly, pre-existing hypertension was associated with increased IgA detection, whereas other cardiovascular diseases were linked to reduced antibody presence at six weeks postpartum. This unexpected finding may reflect disease-specific immune dysregulation or treatment effects [39, 40]. However, the small number of participants with cardiovascular disease limits definitive interpretation and warrants cautious consideration. Further studies are needed to clarify the immunological mechanisms underlying these observations.

Smoking emerged as a negative predictor of IgG presence at delivery, consistent with prior studies showing reduced antibody responses to viral infections [41, 42], and lower SARS-CoV-2 vaccine-induced antibody titres among smokers [43]. Smoking may accelerate antibody decline [42, 44], suggesting that the observed reduction in IgG does not necessarily indicate milder disease. No association was found between smoking and IgA antibodies, possibly reflecting isotype-specific effects or the limited number of smokers in the cohort. These findings support the importance of tobacco cessation interventions in pregnant populations. Multivariable linear regression also identified a modest association between maternal age and postpartum IgG levels ($p=0.044$), with a 2% increase in IgG per additional year of age. This may reflect age-related disease severity [45], although previous studies have reported inverse relationships between maternal age and antibody titres [23, 44]. Notably, despite the high prevalence of gestational diabetes and anaemia in the cohort, neither condition was associated with differential antibody responses, contrary to expectations based on their known effects on immune function [46].

This study has several strengths, including a relatively large sample size, validated methods for SARS-CoV-2 and antibody detection, and comprehensive clinical data enabling a multifactorial analysis. However, as an observational single-centre study, the findings may not be generalisable, and causality cannot be inferred. The study population comprised unvaccinated women infected during the pre-Delta wave, limiting applicability to vaccinated cohorts or those exposed to later variants. Given that vaccination status significantly alters immune responses to SARS-CoV-2 [47, 48], extrapolation to the broader obstetric population should be made with caution. While the association between higher BMI and stronger antibody responses suggests a link between metabolic and immune function, potential confounders – such as diet, physical activity, and socioeconomic status – were not assessed. Additionally, no biochemical markers of inflammation or metabolic status were measured. Antibody profiles were evaluated at only two time points, which may not fully capture the dynamics of humoral immunity during and after pregnancy. Future studies should incorporate longitudinal designs and include a broader panel of immunological and metabolic biomarkers to better characterise the trajectory and mechanisms of SARS-CoV-2 immune responses in pregnant populations.

Conclusions

In this prospective cohort of unvaccinated pregnant women with confirmed SARS-CoV-2 infection, we investigated associations between maternal clinical characteristics and IgG and IgA antibody responses at delivery and 42 days postpartum. Higher preconception BMI was consistently associated with increased odds of detecting both antibody types at both time points, independent of maternal age and comorbidity status. Women without existing comorbidities had lower IgG and IgA levels at delivery, while smoking was associated with reduced IgG detection. Pre-existing cardiovascular disease was linked to lower antibody presence at six weeks postpartum. These findings suggest that overweight, obesity, and chronic comorbidities may influence humoral immune responses in pregnancy, with potential implications for maternal–fetal risk assessment and vaccine responsiveness. Future studies should explore the mechanisms underlying these associations and evaluate their impact on maternal and neonatal outcomes, vertical transmission risk, and immunisation strategies for SARS-CoV-2 and other emerging pathogens in the obstetric population.

Acknowledgments: We thank Vanja Erčulj for her assistance with statistical analysis and Chiedozie Kenneth Ugwoke for his careful proofreading of the manuscript.

Research ethics: The study was approved by the Medical Ethics Committee of the Republic of Slovenia (permit number: 0,120–196/2020-18) and conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Informed consent: Informed consent was obtained from all individuals included in this study.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission. Conceptualization and design: MD, VAM, GK, AI, TPS. Material preparation, data collection, and analysis: MD, VAM, AŠ, TAŽ, GK. Original manuscript drafts: MD. Review and editing: MD, TPS, VAM, GK, AI, TAŽ, AŠ. All authors read and approved the final manuscript.

Use of Large Language Models, AI and Machine Learning Tools: None declared.

Conflict of interest: The authors state no conflict of interest.

Research funding: None declared.

Data availability: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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