BMC Infectious Diseases

RESEARCH

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Seroprevalence and placental transfer of SARS-CoV-2 antibodies in unvaccinated pregnant women

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Abstract

Purpose Pregnant women are at risk of severe SARS-CoV-2 infection, potentially leading to obstetric and neonatal complications. Placental transfer of antibodies directed to SARS-CoV-2 may be protective against neonatal COVID-19, but this remains to be studied. We aimed to determine the seroprevalence of SARS-CoV-2 antibodies in a population of unvaccinated pregnant women and to determine the placental transfer of these antibodies.

Methodology A total of 1197 unvaccinated women with mostly unknown pre-study SARS-CoV-2 infection status, were tested at delivery for SARS-CoV-2 spike protein IgG antibodies during the first year of the pandemic. Umbilical cord samples were collected and assessed for seropositivity if the mother was seropositive. Maternal characteristics, pregnancy and neonatal outcomes and data on SARS-CoV-2 infection were extracted from medical records.

Results Specific IgG were detected in 258 women (21.6%). A significant placental transfer to the newborn was observed in 81.3% of cases. The earlier in the 2nd and 3rd trimesters that the mother had contracted the disease and the more symptomatic she was, the greater the likelihood of transplacental transfer of IgG to her newborn.

Conclusion Approximately one in five women had detectable anti-SARS-CoV-2 spike protein IgG antibodies at delivery during the first year of the pandemic, and these antibodies were significantly transferred to their fetuses. This research provides further evidence to better understand the dynamics of the placental transfer of SARS-CoV-2 IgG antibodies from mothers to their newborns, which is necessary to improve vaccination strategies.

Highlights

- In our large cohort of unvaccinated women, almost ten times the size of the largest previously published study, one in five women had detectable anti-SARS-CoV-2 spike protein IgG antibodies at delivery during the first year of the pandemic.
- Four out of five women transferred these anti-SARS-CoV-2 spike protein IgG antibodies towards their fetuses.

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- The earlier the mother was infected—in the 2nd and 3rd trimester—the higher her antibody level, and the more symptomatic she was, the greater the likelihood of transplacental transfer of IgG to her newborn.
- As placental transfer is variable and depends on several factors, understanding the dynamics of antibody transfer and its impact on fetal health following a natural SARS-CoV-2 infection, can improve vaccination strategies to optimize neonatal protection.

Keywords SARS-COV-2 antibodies, Pregnancy, Seroprevalence, Placental transfer, COVID-19, Antibody

Background

The severe acute respiratory syndrome coronavirus (SARS-CoV-2) has spread rapidly around the world, infecting millions of people. Although pregnant women are not more likely to contract the disease, they are more susceptible to develop a severe infection and maternal and pregnancy complications, depending on the variant [1–7].

Several studies have explored the placental transfer of maternal SARS-CoV-2 specific antibodies following maternal infection, the largest cohort published to date – to our knowledge – evaluated 145 mothers [8–16]. There remains a need for more extensive studies to improve our understanding of the complex dynamics of placental transfer of IgG following natural SARS-CoV-2 infection, which may pave the way for advances in vaccination campaigns [8–12]. Vertical transmission of the virus is rare and usually associated with a favorable neonatal outcome [1, 17].

The majority of SARS-Cov-2 infected patients produce immunoglobin M (IgM), A (IgA) and G (IgG) antibodies against the viral spike (S) and nucleocapsid (N) proteins. Detectable IgM appear 6 to 14 days after the onset of symptoms, while IgG become detectable one to three weeks later. IgG reach high titers, decline within two months and then remain relatively stable for the next 6 to 12 months [18, 19].

The fetus produces IgG and IgM antibodies from approximately 20 weeks of gestation. Maternal IgG antibodies are transferred across the placenta to the fetus from the end of the first trimester of pregnancy onwards [20–23], so most of the fetal IgG antibodies are of maternal origin [24]. Gestational age (GA), IgG subclass (highest for IgG1 and lowest for IgG2), antigen specificity, Fc IgG glycosylation, maternal antibody concentration, chronic maternal infection, placental pathology are factors that can influence placental transfer [21, 23, 25–27]. IgM antibodies, on the other hand, do not cross the placenta. If present in the fetal blood, they are deemed to have been produced by the fetus in response to an in utero exposure to SARS-CoV-2, strongly suggesting intrauterine infection [9, 24, 28]. However, cord blood IgM assays are prone to false-positive results due to cross-reactivity or to interference caused by sample contamination with maternal blood or increased permeability of the syncytiotrophoblast barrier due to infection-induced inflammation [10, 29].

Objectives

The first objective of our study was to report the seroprevalence of SARS-CoV-2 specific IgG antibodies against S protein in unvaccinated pregnant women during the first year of the pandemic. The second objective was to assess the placental transfer of IgG S SARS-CoV-2 antibodies and their determinants and the prevalence of IgM antibodies in the umbilical cord (UC).

Study design

This prospective, multicenter observational study was conducted between August 18, 2020, and April 2, 2021.

Pregnant women who were admitted for delivery after 35 weeks gestation to Erasme University Hospital (an academic tertiary hospital with about 2000 deliveries per year) or Delta Hospital (a general secondary hospital with about 3500 deliveries per year) in Brussels (Belgium) during the study period were invited to participate. A total of 1207 pregnant women and their newborns were enrolled in the study. Ten cases were excluded from the analysis for the following reasons: duplication (eight cases); no laboratory sample received (one case); incorrect labelling of blood samples (one case).

At the time of enrollment, we obtained informed consent from the participating women and collected blood samples for the measurement of SARS-CoV-2 spike-specific antibodies. In addition, after delivery, whether by delayed or immediate umbilical cord clamping, we collected cord blood samples for the assessment of SARS-CoV-2 specific antibodies. Both blood samples were stored in the BioBank of the National Reference Centre for Congenital Infections and form the Covid VERtical Transmission (CoVerT) cohort.

Detailed information was extracted from the medical records using a standardized data collection form. Data were recorded anonymously in a REDCap database (Research Electronic Data Capture) [30]. For each included case, maternal characteristics (sociodemographic characteristics, past medical history, height, weight, pregnancy complications, obstetric outcome),

information on maternal SARS-CoV-2 infection (nasopharyngeal polymerase chain reaction test (PCR), symptoms, hospitalization, imaging, intensive care unit (ICU) admission, oxygen therapy) and neonatal characteristics (birth parameters, neonatal outcome, admission to the neonatal ICU mode of feeding, length of hospital stay) were recorded.

Serological testing was performed using the DiaSorin test on the LIAISON XL analyzer. These tests are based on the detection of antibodies against the spike protein (S), anchored in the viral envelope. Specific IgG were measured against both subunits of the spike protein S1 and S2. These proteins are, respectively, responsible for the binding (S1) and fusion (S2) of the virus to the cell. Only IgM antibodies directed against S1 were evaluated. The diagnostic sensitivity and specificity of the LIAISON SARS-CoV-2 IgM assay were 98.3% (95% CI: 93.9%—99.5%) and 99.2% (95% CI: 98.0%—99.7%), respectively [31]. The IgM cut-off was set at 1.10 AU/mL according to the manufacturer's recommendations. A performance study of the LIAISON SARS-CoV-2 S1/S2 IgG test indicated that the cut-off for IgG positivity was 6.1 AU/mL [31], and we used this cut-off for our study. The specificity and sensitivity using this threshold were 99% (95% CI: 93.0%—100.0%) and 100% (95% CI: 92.0%—100.0%), respectively [31]. All maternal blood samples were tested for IgG. UC samples were tested for IgG and IgM if the maternal result was positive.

Grand multiparity was defined as a participant having given birth three times or more. A seropositive mother is one who tested positive for specific SARS-CoV-2 IgG antibodies in her blood. In our study, a seropositive newborn is defined as an infant whose umbilical cord blood tested positive for specific SARS-CoV-2 IgG antibodies.

The placental transfer ratio (PTR) was calculated as the level of IgG antibodies in UC blood divided by the level of maternal IgG antibodies.

Statistical analyses were performed using STATA version 17 (Statacorp, TX, USA). Descriptive analyses were performed with presentation of numbers and proportions (categorical variables); for quantitative variables mean and standard deviation (in case of a normal distribution), median with interquartile range (in case of an abnormal distribution of the variables) were calculated. For categorical variables, bivariable comparisons were made using the Chi^2 or Fisher's exact tests, and for continuous variables, a t-test (two groups) in case of a normal distribution of variables and a Mann–Whitney test (two groups) in case of an abnormal distribution of variables. Multivariable modeling was performed to predict maternal seroprevalence and to identify factors independently associated with the placental transfer. Factors were included in the model if there was an association with a p-value < 0.2 in the univariate analysis. Statistical significance was defined as a p-value < 0.05 and we report the 95% confidence interval (CI).

The study was approved by the central ethics committee of the Erasme University Hospital (ULB) (P2020/396) and by the local ethics committee of the Delta Hospital.

Results

Study population

A total of 1197 unvaccinated pregnant women were included in the study. Sociodemographic characteristics are shown in Table 1. The prevalence of positive maternal IgG was higher in women from sub-Saharan Africa (odds ratio OR 2.69) and North Africa (OR 2.16), compared to women from Northern Europe ($p = 0.001$). IgG-positive participants were more likely to be large multiparas (OR 2.77 compared to nulliparas). No other sociodemographic differences were observed between participants who were positive or negative for IgG against the SARS-CoV-2 spike protein.

Pregnancy characteristics and obstetric outcomes are shown in Table 2. The median GA at delivery was 39 weeks, ranging from 35 weeks 0 days to 42 weeks 2 days. No maternal death was reported. One neonate died from a congenital heart defect (Table 3).

Prevalence of maternal IgG antibodies

A total of 258 women out of 1197 (21.6%) had SARS-CoV-2 S protein spike antibodies when they were admitted to the labor ward (Fig. 1).

We have observed no difference between seropositive and seronegative mothers in terms of mode of delivery or GA at birth. Seropositive mothers were more likely to have pregnancy complications (OR 1.38) and cumulative pregnancy complications ($p = 0.004$) (Table 2). Neonatal outcomes were similar between the two groups (Table 3). We observed a statistically significant difference in birth weight between the two groups; neonates born from seropositive mothers had a lower birth weight (mean 3375 g) compared to the ones born from seronegative mothers (mean 3436 g) ($p = 0.04$), even after adjustment for confounders.

A total of 48.7% (503/1197) participants underwent a PCR testing, mostly on admission or the day before. Among seronegative women, 3.1% of women tested positive compared with 40.4% among seropositive women ($p < 0.001$) (Table S1).

Ninety newborns (7.6%) were tested by nasopharyngeal SARS-CoV-2 PCR in the immediate postpartum period guided by local policies and clinical discretion; 38 (42.2%) were positive, all of these infants were born to IgG-positive mothers.

Table 1 Sociodemographic characteristics of the participants. Comparison between mothers with and without anti-SARS-CoV-2 spike protein IgG antibodies detected

Characteristics	ALL n (%)	Maternal IgG positive	Maternal IgG negative	*p* value (OR)
Maternal age	1197	258	939	0.1*
18–24	46 (3.8)	14 (5.4)	32 (3.4)	
25–29	275 (23.0)	62 (24.0)	213 (22.7)	
30–34	517 (43.2)	116 (45.0)	401 (42.7)	
35–39	275 (23.0)	45 (17.5)	230 (24.5)	
40 or more	84 (7.0)	21 (8.1)	63 (6.7)	
Smoking (14 missing data)				
Yes	50 (4.2)	11 (4.3)	39 (4.2)	1.0*
Drug abuse (13 missing data)				
Yes	4 (0.3)	0	4 (0.4)	0.6*
Origin				**0.001***
Northern Europe	799 (66.8)	152 (58.9)	647 (68.9)	ref
Mediterranean region	182 (15.2)	36 (14.0)	146 (15.6)	OR 1.05 CI [0.70–1.57]
Northern Africa	104 (8.7)	35 (13.6)	69 (7.4)	**OR 2.16 CI [1.39–3.36]**
Sub-Saharan Africa	62 (5.2)	24 (9.3)	38 (4.0)	**OR 2.69 CI [1.56–4.62]**
Other	50 (4.2)	11 (4.2)	39 (4.1)	OR 1.20 CI [0.60–2.40]
BMI (39 missing data)				
Underweight (< 18.5)	54 (5.1)	11 (4.9)	43 (5.2)	0.5*
Normal weight (18.5 – 25)	719 (68.0)	150 (66.7)	569 (68.3)	
Overweight (25 – 30)	187 (17.7)	37 (16.4)	150 (18.0)	
Obese (≥ 30)	98 (9.3)	27 (12.0)	71 (8.5)	
Medical history				
Hypertension	9 (0.8)	3 (1.2)	6 (0.6)	0.4
Pre-existing diabetes	6 (0.5)	1 (0.4)	5 (0.5)	1.0
Asthma	56 (4.7)	12 (4.7)	44 (4.7)	1.0
Poor obstetric history				
Late miscarriage	8/1193 (0.7)	2/258 (0.8)	6/935 (0.6)	0.7*
Stillbirth	9/1187 (0.8)	2/255 (0.8)	7/932 (0.8)	1.0*
Preterm birth < 32 weeks	6/1186 (0.5)	2/256 (0.8)	4/930 (0.4)	0.6*
Preterm birth < 37 weeks	23/1192 (1.9)	5/255 (2.0)	18/937 (1.9)	1.0*
Parity				**0.004***
Nulliparity	621 (51.9)	122 (47.3)	499 (53.1)	ref
Multiparity 1–2	524 (43.8)	115 (44.6)	409 (43.6)	**OR 1.1 CI [0.86–1.53]**
Grand multiparity (> = 3)	52 (4.3)	21 (8.1)	31 (3.3)	**OR 2.77 CI [1.54–4.99]**

Abbreviations: *BMI* Body mass index, *CI* Confidence interval, *IgG* Immunoglobulin of type G, *OR* Odds ratio, *ref* Reference

* Fischer's exact test

After adjustment, maternal seropositivity was associated with North African origin (aOR 2.2), large multiparity (aOR 2.8) and history of a positive PCR test for SARS-CoV-2 (aOR 28.7). When no SARS-CoV-2 PCR test was performed, maternal age also influenced seropositivity. Each additional year of maternal age, reduced the risk of seropositivity by 0.05% (Table S2).

Placental transfer of IgG antibodies

In 209 out of 257 umbilical cord samples collected from seropositive women tested at birth, we detected the presence of IgG antibodies (81.3%) (Fig. 1). When we compared the two subgroups (positive or negative IgG in the UC), no statistically significant differences were found in sociodemographic and maternal characteristics or obstetric outcomes (Table S3-4).

We observed a statistically significant difference in maternal IgG levels between the group of women who had transferred their antibodies to their newborns and those who did not (median IgG level 20.5 AU/ml versus 7.3 AU/ml) (OR 1.2; $p < 0.001$) (Table 4). Mothers with maternal symptoms suggestive of SARS-CoV-2

Table 2 Pregnancy and obstetric outcomes. Comparison between participants with and without maternal anti- SARS-CoV-2 spike protein IgG antibodies

Characteristics	ALL n (%)	Maternal IgG positive (*n* = 258)	Maternal IgG negative (*n* = 939)	*p* value OR
Pregnancy complications				
None	641 (53.6)	122 (47.3)	519 (55.3)	**0.02**[*]
Risk premature birth	38 (3.2)	11 (4.3)	27 (2.9)	0.3[*]
PPROM	11 (0.9)	1 (0.4)	10 (1.1)	0.9[^]
Gestational diabetes with diet	94 (7.9)	20 (7.8)	74 (7.9)	0.9[*]
Gestational diabetes with insulin	49 (4.1)	10 (3.9)	39 (4.2)	0.8[*]
Gestational hypertension	17 (1.4)	7 (2.7)	10 (1.1)	0.07[^]
Preeclampsia / HELLP / Eclampsia	25 (2.1)	6 (2.3)	19 (2.0)	0.8[*]
Thrombocytopenia	14 (1.2)	2 (0.8)	12 (1.3)	0.7[^]
Postpartum hemorrhage	17 (1.4)	7 (2.7)	10 (1.1)	0.4[*]
Cumulative pregnancy complications				**0.004**[^]
0	654 (54.6)	124 (48.1)	530 (56.4)	ref
1	419 (35.0)	95 (36.8)	324 (34.5)	**OR 1.25** CI[0.93–1.69]
2	103 (8.6)	29 (11.2)	74 (7.9)	**OR 1.67** CI[1.04–2.68]
> 2	21 (1.8)	10 (3.9)	11 (1.2)	**OR 3.88** CI[1.61–9.35]
Type of birth (3 missing data)				
Vaginal birth	924 (77.4)	206 (80.5)	718 (76.6)	0.6[^]
Instrumental birth	166 (13.9)	33 (12.9)	133 (14.2)	
Primary C-section	18 (1.5)	3 (1.2)	15 (1.6)	
Secondary C-section	86 (7.2)	14 (5.5)	72 (7.7)	
Gestational age at birth (4 missing data)				
< 37 weeks	19 (1.6)	2 (0.8)	17 (1.8)	0.3[^]
37 < 38 weeks	71 (6.0)	19 (7.4)	52 (5.6)	
38 < 39 weeks	192 (16.1)	41 (16.0)	151 (16.1)	
39 < 40 weeks	323 (27.1)	80 (31.3)	243 (25.9)	
40 < 41 weeks	402 (33.7)	80 (31.3)	322 (34.3)	
> 41 weeks	186 (15.5)	34 (13.3)	152 (16.2)	

Cumulative pregnancy complications: sum of the pregnancy complications

Abbreviations: *CI* Confidence interval, *C-section* Caesarean section, *HELLP* Hemolysis elevated liver enzymes low platelets, *IgG* Immunoglobulins G, *OR* Odds ratio, *pPROM* Preterm premature rupture of membranes, *ref* Reference

[*] Chi2 test

^Fisher's exact test

infection were also more likely to have transferred their IgG (OR 3.8; $p = 0.04$) compared to asymptomatic mothers.

In our cohort, only three women were hospitalized for SARS-CoV-2 infection during pregnancy and all of them transferred IgG antibodies to their newborns.

Two women with worsening symptoms in the postpartum period were admitted to ICU with oxygen therapy. In these two cases, the PCR tests were positive eight and three days before delivery and maternal IgG levels were 20 and 15 AU/ml, respectively. Neonatal IgG levels were negative in both cases (Table 4).

The level of IgG in the UC was correlated with the level of IgG in the mother (rho 0.84; $p < 0.001$). There was also a correlation with the cumulative number of maternal pregnancy complications (rho 0.24; $p < 0.001$), with the interval between a positive maternal PCR for SARS-CoV-2 and delivery (rho 0.28; $p = 0.02$) and with the cumulative number of symptoms (rho 0.18; $p = 0.004$).

Mothers who tested positive by PCR less than one week before to delivery had a median IgG level of 6.4 U/mL, with 25% of infants being seronegative. In contrast, among participants who infected more than four weeks prior to birth, the median IgG level at delivery was 20.5 U/mL, and we observed that 96% of infants had detectable IgG in cord blood. Seronegative newborns were observed to have a shorter interval between

Table 3 Neonatal outcomes. Comparison between participants with and without maternal anti- SARS-CoV-2 spike protein IgG antibodies

Characteristics	ALL n (%)	Maternal IgG positive (*n* = 258)	Maternal IgG negative (*n* = 939)	*p* value
Apgar 5 min < 7	14 (1.2)	3 (1.2)	11 (1.2)	1.0^
pH < = 7.0	7 (0.6)	0	7 (0.8)	0.5^
NICU admission	59 (4.9)	17 (6.6)	42 (4.5)	0.2°
Length neonatal stay (median, (IQR)	(3.0 (1.0))	(3.0 (1.0))	(3.0 (1.0))	
Breastfeeding				
Yes, exclusively	975 (82.6)	213 (83.2)	762 (82.4)	0.9*
Yes, but mixed	92 (7.8)	18 (7.0)	74 (8.0)	
No, artificial feeding	114 (9.7)	89 (9.6)	89 (9.6)	
Birthweight (gram)				
Mean (se)	3422.7 (12.5)	3435.9 (14.0)	3374.6 (27.1)	0.04#
Neonatal death	1 (0.08)	1 (0.1)	0	1.0 ^

Abbreviations: *IQR* inter quartile range, *se* standard error

* Chi2 test

^ Fisher's exact test

° Mann–Whitney test

Student t-test

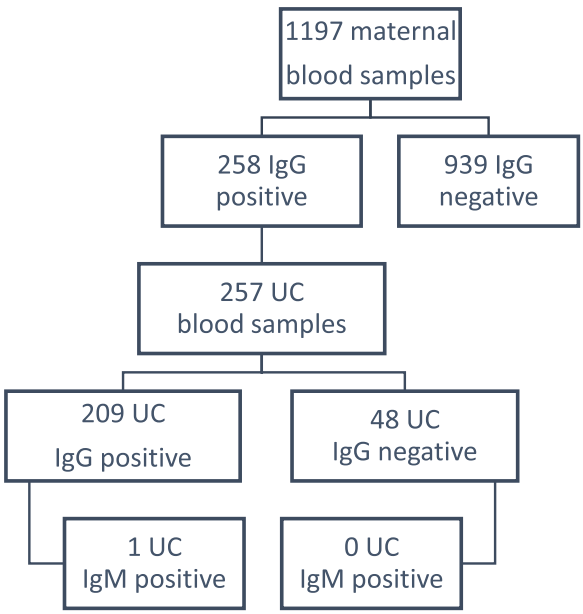

Fig. 1 Flowchart representing detected antibodies in blood samples of participants. Abbreviations: IgM = immunoglobulin M; IgG = immunoglobulin G; UC = umbilical cord

maternal PCR positivity and delivery than seropositive newborns.

Placental transfer ratio

The median PTR was 1.05, with the highest value of 2.8 (Fig. 2). The longer the delay between a PCR-positive test and delivery, the higher the PTR ($p < 0.001$). Additionally, the PTR increased with younger GA at the time of the PCR-positive test ($p = 0.02$); each additional day increased the PTR by 0.003 ($p < 0.001$).

Vertical transmission

Of 209 UC samples acquired from 257 mothers who tested positive for IgG, only one newborn tested positive for IgM antibodies (IgM 2.83 AU/mL) against SARS-CoV-2 S1 (0.4%). This newborn IgG level was 71.2 AU/mL. The mother, a primiparous woman in good health, tested negative for IgM (Figure S1). We have not performed confirmatory testing and cannot rule out the possibility of a false positive IgM result due to interference or cross-reactivity.

Discussion

Maternal seroprevalence

The seroprevalence of SARS-CoV-2 specific IgG antibodies in our study population was 21.6%. This percentage aligns with the findings of other studies of unvaccinated women carried out in different regions during the initial wave of the coronavirus disease (COVID-19) pandemic [32–34]. Maternal seropositivity was associated with grand multiparity and maternal origin from Northern or Sub-Saharan Africa. The elevated risk observed in grand multiparous women may be attributed to their increased exposure to potential sources of infection. After adjusting for confounding factors, we found that North African origin was associated with a higher risk of maternal

Table 4 Association between placental transfer of IgG and variables related to the SARS-CoV2 infection in IgG positive mothers

Umbilical cord samples from women seropositive for SARS-CoV-2					
Variables related to SARS-CoV-2 infection	**UC IgG positive (*n* = 209; 81.3%)**		**UC IgG negative (*n* = 48; 18.7%)**		***P* value OR**
	n (%)	**Median (IQR)**	**n (%)**	**Median (IQR)**	
Median maternal IgG level (U/mL)		20.5 (11.6–37.2)		7.3 (6.8–9.4)	**< 0.001**[a] **OR 1.2**
Symptoms					
Yes	38 (18.2)		3 (6.3)		**0.04**[b]
No	171 (81.8)		45 (93.7)		**OR 3.3**
Number of symptoms					
0	171 (81.8)		45 (93.7)		0.37[d]
1	17 (7.7)		2 (4.2)		
2	5 (2.4)		1 (2.1)		
3	6 (2.9)		0		
4 or more	10 (4.8)		0		
Maternal nasopharyngeal PCR*	*n* = 148		*n* = 17		1.0[b]
Positive	62 (41.9)		7 (41.2)		
Negative	86 (58.1)		10 (58.8)		
Gestational age when the maternal PCR was positive	*n* = 57		*n* = 7		0.4[d]
Median (in weeks)		28 (25–33)		36 (32–39)	
< 14 weeks	2 (3.5)		0		
14 to 28 weeks	24 (42.1)		1 (14.3)		
28 to 41 weeks	31 (54.4)		6 (85.7)		
Interval between maternal positive PCR and birth	*n* = 57		*n* = 7		0.7[d]
Median (in days)		78 (36–102)		21 (4–39)	
0 ≥ 91 days	37 (64.9)		6 (85.7)		
91 ≥ 182 days	18 (31.6)		1 (14.3)		
> 182 days	2 (3.5)		0		
Maternal hospitalization for SARS-CoV-2 infection					
Yes	3 (1.4)		0		1.0[d]

Abbreviations: *IgG* Immunoglobulins G, *IQR* Interquartile range, *OR* Odds ratio, *PCR* Polymerase chain reaction, *UC* Umbilical cord

[a] Wilcoxon-Mann–Whitney test

[b] Chi^2 test

[c] Kruskal-Wallis test

[d] Fischer's exact test

seropositivity. A meta-analysis including 18,728,893 participants, suggests that ethnicity may contribute to the likelihood of contracting SARS-CoV-2 infection [35]. Although, some other possible confounders, e.g. large households, respect or not of preventive measures were not investigated.

Placental transfer of IgG

Our CoVerT cohort showed significant placental transfer of antibodies (81%), consistent with findings from smaller cohort studies [6, 7, 15, 23, 25, 26]. Newborns testing positive for antibodies at umbilical cord were linked with elevated maternal IgG levels, a longer interval between infection and delivery, maternal infection occurred during the early stages of the second and third trimesters of pregnancy, and an accumulation of maternal COVID-19 symptoms [9, 10, 36, 37].

In our cohort, most women were asymptomatic, with imprecise timing of infection. Whenever timing could be estimated, seronegative newborns were born to mothers with a positive PCR test later in pregnancy compared to those who were seropositive. When pregnant women contract COVID-19 towards the end of the pregnancy, maternal IgG antibodies may still be rising, resulting in potentially lower IgG transfer to the fetus [22, 36, 38, 39]. The absence of antibodies observed in newborns of seropositive mothers who contracted infection in the last four weeks of pregnancy, may be attributed to the possible

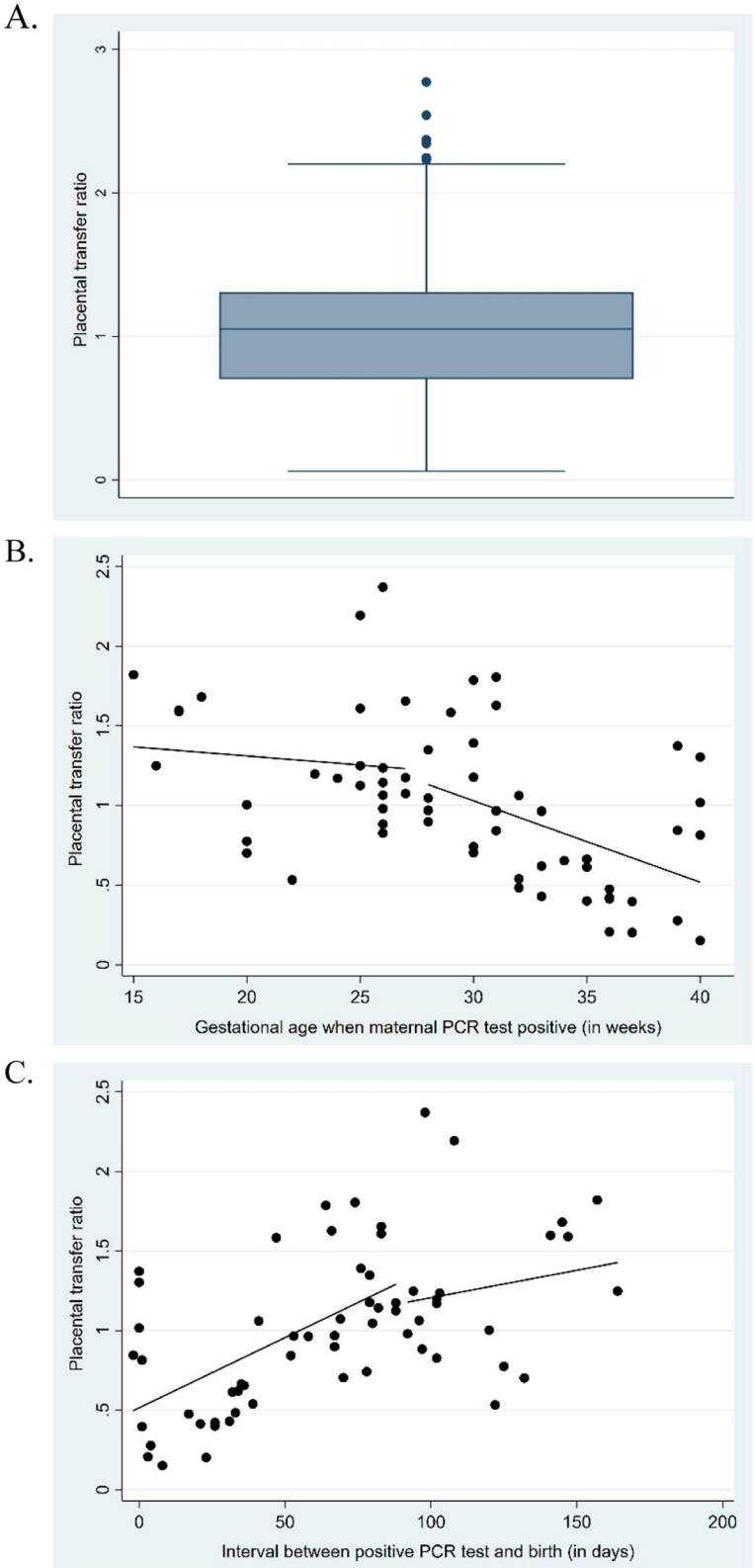

Fig. 2 Placental transfer ratio. **a** The box plot showing the placental transfer ratio of all cases. **b** Scatter plot illustrating the relationship between placental transfer ratio and gestational age (in weeks) at which a positive PCR was detected (focusing on the second and third trimesters only). **c** Scatter plot illustrating the relationship between placental transfer ratio and the number of days between birth and positive PCR test result

alteration of the Fc glycosylation of SARS-CoV-2 IgG antibodies, influenced by early inflammatory responses [21, 23, 26, 27, 40, 41]. It has been suggested that this modification may normalize gradually over time [22, 26, 27, 37], thereby enabling the typical placenta antibody transfer when there is a sufficient interval between infection and delivery.

In our cohort, the median PTR was calculated at 1.05. A higher PTR was consistently observed when maternal SARS-CoV-2 infection occurred earlier in the second or third trimester, particularly when there was a longer interval between the positive PCR test and delivery, but still within the second and third trimesters. These findings align with previous studies [8, 37, 40] that have reported similar trends in PTR variation concerning the timing of infection and delivery [22, 42, 43]. Due to limitations in our data, we were unable to analyze PTR values for infections occurring in the first trimester.

By understanding the dynamics of antibody transfer and their implications for fetal health following a natural SARS-CoV-2 infection, we can improve vaccination strategies to optimize protection for neonates.

Strengths and limitations

Our study has some limitations. The timing of SARS-CoV-2 infection, and subsequent antibody production onset, remains unknown. We conducted a retrospective review of medical records, which limited our ability to assess COVID-19 symptoms during pregnancy.

Although comparable between the two groups of women, complication rates were low in both groups: caesarean section (8.7%) and prematurity (1.3%). Participation in the trial had not been systematically offered to women presenting with preterm labor or with a planned cesarean section.

We did not perform a PCR-based diagnostic test for SARS-CoV-2 on all newborns at birth, as this test was considered too invasive to be performed routinely. Furthermore, the clinical interpretation of results in newborns is not always straightforward, due to maternal contamination [44].

Our data from a cohort of unvaccinated pregnant women more than two years ago may be of less clinical value now, but our CoVerT cohort remains the largest group of pregnant women and their newborns who have undergone SARS-CoV-2 antibody testing at birth. Worldwide, not all women who are pregnant or hoping to become pregnant have access to vaccination.

The extensive data on sociodemographic and clinical outcomes for pregnant women and neonates is a solid advantage of this study. In addition, none of the women in our study were vaccinated, which allowed the analysis of antibodies induced solely by natural infection.

Conclusion

In our study of a cohort of unvaccinated pregnant women who gave birth in Belgian maternities after 35 weeks of pregnancy during the initial year of the COVID-19 pandemic, we found that about one in five women had detectable anti-SARS-CoV-2 spike protein IgG antibodies at the time of delivery. We showed that transplacental transfer of SARS-CoV-2 IgG was significant, particularly when the maternal infection was more severe, occurred earlier in 2nd or 3rd trimester of pregnancy or resulted in higher IgG titers. Only one newborn was found to have IgM in cord blood. These findings provide evidence that maternal anti-SARS-CoV-2 IgG molecules are transferred to the fetus. This underscores the importance of vaccination during pregnancy as a potential strategy to protect newborns against SARS-CoV-2 infection.

Abbreviations

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
IgG	Immunoglobulin type G
IgA	Immunoglobulin type A
IgM	Immunoglobulin type M
S	Spike protein
N	Nucleocapsid (protein & RNA genome)
GA	Gestational age
IgG1	Immunoglobulin type G subtype 1
IgG2	Immunoglobulin type G subtype 2
UC	Umbilical cord
CoVerT	Covid VERtical Transmission
REDCap	Research Electronic Data Capture
PCR	Polymerase chain reaction
ICU	Intensive care unit
sd	Standard deviation
OR	Odds ratio
aOR	Adjusted odds ratio
COVID-19	Coronavirus disease 2019

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-09399-6.

Supplementary Material 1.

Acknowledgements

We thank all the patients for the kind donation of samples, the midwives and doctors for their collection and the Fonds National pour la Recherche Scientifique (FNRS) for their support.
The authors are indebted to Dominique Slechten, Catherine Radelet and Chloé Taelman for their help encoding the data.
A special thanks to Professor Françoise Vermeulen (H.U.B. Erasme) for assistance in raising funding, to Professor Anne Delbaere (H.U.B. Erasme) for enabling participation to the study, to Dansala Welba of the Institute for Medical Immunology ULB for his help in creating the graphs, and to the laboratory assistants for their thorough work.

Authors' contributions

Conceptualization, A.V., M.Z., S.H., M.L.D, C.D. and D.K.; methodology, A.V., M.Z., M.B., M.L.D., C.D. and D.K.; data collection A.V., M.T., S.H., M.L.D., C.D. and D.K; formal analysis, A.V., M.Z., M.T., M.B., L.DD, M.L.D., C.D. and D.K.; investigation, A.V.,; writing—original draft preparation, A.V, M.Z., M.T., M.B., M.L.D., C.D. and D.K. writing—review and editing, A.V, M.Z., M.T., J.G., M.B., L.D.D., S.D., S.H., M.L.D., C.D. and D.K.; figures, A.V., M.Z. and L.D.D; supervision, J.G., M.B., M.L.D.,

C.D. and D.K. All authors have read and agreed to the published version of the manuscript.

Funding
This work was supported by the Fonds de la Recherche Scientifique (FNRS) (grant number FNRS CUR – 40002813, 2020).

Availability of data and materials
Data is provided within the manuscript or supplementary information files. Data cannot be shared publicly because of confidentiality issues and potential identifiability of sensitive data as identified within the Research Ethics Committee application / approval. Requests to access the data can be made by contacting an.vercoutere@hubruxelles.be.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki, and approved by a central Ethics Committee of the Erasme University Hospital (ULB) (P2020/396) and by the local ethics committee of the Delta Hospital. Informed consent to participate was obtained from all participants.

Consent for publication
Informed consent to publish was obtained from all participants.

Competing interests
The authors declare no competing interests.

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Received: 18 December 2023 Accepted: 13 May 2024
Published online: 21 May 2024

References

1. Vousden N, Bunch K, Morris E, Simpson N, Gale C, O'Brien P, et al. The incidence, characteristics and outcomes of pregnant women hospitalized with symptomatic and asymptomatic SARS-CoV-2 infection in the UK from March to September 2020: A national cohort study using the UK Obstetric Surveillance System (UKOSS). Farrar D, editor. PLoS One. 2021;16(5):e0251123 (https://dx.plos.org/10.1371/journal.pone.0251123).
2. 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:m2107.
3. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020;370:m3320.
4. Favre G, Maisonneuve E, Pomar L, Daire C, Poncelet C, Quibel T, et al. Maternal and perinatal outcomes following pre-Delta, Delta, and Omicron SARS-CoV-2 variants infection among unvaccinated pregnant women in France and Switzerland: a prospective cohort study using the COVI-PREG registry. Lancet Reg Heal - Eur. 2023;26:100569. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2666776222002654.
5. de Bruin O, Engjom H, Vousden N, Ramakrishnan R, Aabakke AJM, Äyräs O, et al. Variations across Europe in hospitalization and management of pregnant women with <scp>SARS-CoV</scp> -2 during the initial phase of the pandemic: Multi-national population-based cohort study using the International Network of Obstetric Survey Systems (<. Acta Obstet Gynecol Scand. 2023; Available from: https://doi.org/10.1111/aogs.14643.
6. Stock SJ, Moore E, Calvert C, Carruthers J, Denny C, Donaghy J, et al. Pregnancy outcomes after SARS-CoV-2 infection in periods dominated by delta and omicron variants in Scotland: a population-based cohort study. Lancet Respir Med. 2022;10(12):1129–36. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213260022003605.
7. Villar J, Soto Conti CP, Gunier RB, Ariff S, Craik R, Cavoretto PI, et al. Pregnancy outcomes and vaccine effectiveness during the period of omicron as the variant of concern, INTERCOVID-2022: a multinational, observational study. Lancet. 2023;401(10375):447–57. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673622024679.
8. Flannery DD, Gouma S, Dhudasia MB, Mukhopadhyay S, Pfeifer MR, Woodford EC, et al. Assessment of Maternal and Neonatal Cord Blood SARS-CoV-2 Antibodies and Placental Transfer Ratios. JAMA Pediatr. 2021;175(6):594. Available from: https://jamanetwork.com/journals/jamapediatrics/fullarticle/2775945.
9. Kubiak JM, Murphy EA, Yee J, Cagino K, Friedlander RL, Glynn SM, et al. SARS-CoV-2 serology levels in pregnant women and their neonates. Am J Obstet Gynecol. 2021; Available from: http://www.ncbi.nlm.nih.gov/pubmed/33497654.
10. Mahyuddin AP, Kanneganti A, Wong JJL, Dimri PS, Su LL, Biswas A, et al. Mechanisms and evidence of vertical transmission of infections in pregnancy including SARS-CoV-2s. Prenat Diagn. 2020;40(13):1655–70.
11. Raschetti R, Vivanti AJ, Vauloup-Fellous C, Loi B, Benachi A, De Luca D. Synthesis and systematic review of reported neonatal SARS-CoV-2 infections. Nat Commun. 2020;11(1). https://doi.org/10.1038/s41467-020-18982-9.
12. Ben-Hur H, Gurevich P, Elhayany A, Avinoach I, Schneider D, Zusman I. Transport of maternal immunoglobulins through the human placental barrier in normal pregnancy and during inflammation. Int J Mol Med. 2005; Available from: http://www.spandidos-publications.com/https://doi.org/10.3892/ijmm.16.3.401.
13. Song D, Prahl M, Gaw SL, Narasimhan SR, Rai DS, Huang A, et al. Passive and active immunity in infants born to mothers with SARS-CoV-2 infection during pregnancy: prospective cohort study. BMJ Open. 2021;11(7):e053036. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34234001.
14. Matsui Y, Li L, Prahl M, Cassidy AG, Ozarslan N, Golan Y, et al. Neutralizing antibody activity against SARS-CoV-2 variants in gestational age-matched mother-infant dyads after infection or vaccination. JCI insight. 2022;7(12). Available from: http://www.ncbi.nlm.nih.gov/pubmed/35579965.
15. Vigil-Vázquez S, Manzanares Á, Hernanz-Lobo A, Carrasco-García I, Zamora Del Pozo C, Pérez-Pérez A, et al. Serologic evolution and follow-up to IgG antibodies of infants born to mothers with gestational COVID. BMC Pregnancy Childbirth. 2023;23(1):623. Available from: http://www.ncbi.nlm.nih.gov/pubmed/37648971.
16. Helguera-Repetto AC, Villegas-Mota I, Arredondo-Pulido GI, Cardona-Pérez JA, León-Juárez M, Rivera-Rueda MA, et al. Cord Blood SARS-CoV-2 IgG Antibodies and Their Association With Maternal Immunity and Neonatal Outcomes. Front Pediatr. 2022;10:883185. Available from: http://www.ncbi.nlm.nih.gov/pubmed/35844759.
17. Allotey J, Chatterjee S, Kew T, Gaetano A, Stallings E, Fernández-García S, et al. SARS-CoV-2 positivity in offspring and timing of mother-to-child transmission: living systematic review and meta-analysis. BMJ. 2022;e067696. Available from: https://www.bmj.com/lookup/doi/https://doi.org/10.1136/bmj-2021-067696.
18. Walls AC, Park Y-J, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell. 2020;181(2):281–292.e6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0092867420302622.
19. Havervall S, Ng H, Jernbom Falk A, Greilert-Norin N, Månberg A, Marking U, et al. Robust humoral and cellular immune responses and low risk for reinfection at least 8 months following asymptomatic to mild COVID-19. J Intern Med. 2022;291(1):72–80. Available from: https://onlinelibrary.wiley.com/doi/https://doi.org/10.1111/joim.13387.

20. Kohler PF, Farr RS. Elevation of Cord over Maternal IgG Immunoglobulin: Evidence for an Active Placental IgG Transport. Nature. 1966;210(5040):1070–1. Available from: https://www.nature.com/articles/2101070a0.
21. Chu HYI aspects of vaccines in pregnancy: maternal perspective, Marchant A. Immunobiological aspects of vaccines in pregnancy: maternal perspective. In: Maternal immunization. 2020. p. 377.
22. Atyeo C, Pullen KM, Bordt EA, Fischinger S, Burke J, Michell A, et al. Compromised SARS-CoV-2-specific placental antibody transfer. Cell. 2021;184(3):628–642.e10. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0092867420317499.
23. Jennewein MF, Abu-Raya B, Jiang Y, Alter G, Marchant A. Transfer of maternal immunity and programming of the newborn immune system. Semin Immunopathol. 2017;39(6):605–13. https://doi.org/10.1007/s00281-017-0653-x.
24. Auriti C, De Rose DU, Tzialla C, Caforio L, Ciccia M, Manzoni P, et al. Vertical Transmission of SARS-CoV-2 (COVID-19): Are Hypotheses More than Evidences? Am J Perinatol. 2020;37(8):S31–8.
25. Nielsen SY, Petersen LH, Murra M, Hvidman L, Helmig RB, Møller JK, et al. Transplacental transfer of SARS-CoV-2 antibodies: a cohort study. Eur J Clin Microbiol Infect Dis. 2023;42(3):277–85. https://doi.org/10.1007/s10096-023-04553-5.
26. Jennewein MF, Goldfarb I, Dolatshahi S, Cosgrove C, Noelette FJ, Krykbaeva M, et al. Fc Glycan-Mediated Regulation of Placental Antibody Transfer. Cell. 2019;178(1):202–215.e14. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0092867419306154.
27. Wilcox CR, Holder B, Jones CE. Factors Affecting the FcRn-Mediated Transplacental Transfer of Antibodies and Implications for Vaccination in Pregnancy. Front Immunol. 2017;8. Available from: http://journal.frontiersin.org/article/https://doi.org/10.3389/fimmu.2017.01294/full.
28. Egerup P, Fich Olsen L, Christiansen A-MH, Westergaard D, Severinsen ER, Hviid KVR, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Antibodies at Delivery in Women, Partners, and Newborns. Obstet Gynecol. 2021;137(1):49–55. Available from: https://journals.lww.com/https://doi.org/10.1097/AOG.0000000000004199.
29. Delforge ML, Desomberg L, Montesinos I. Evaluation of the new LIAISON ® CMV IgG, IgM and IgG Avidity II assays. J Clin Virol. 2015;72:42–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1386653215006691.
30. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1532046408001226.
31. Tré-Hardy M, Wilmet A, Beukinga I, Dogné J-M, Douxfils J, Blairon L. Validation of a chemiluminescent assay for specific SARS-CoV-2 antibody. Clin Chem Lab Med. 2020;58(8):1357–64. https://doi.org/10.1515/cclm-2020-0594/html.
32. Villalaín C, Herraiz I, Luczkowiak J, Pérez-Rivilla A, Folgueira MD, Mejía I, et al. Seroprevalence analysis of SARS-CoV-2 in pregnant women along the first pandemic outbreak and perinatal outcome. PLoS One. 2020;15(11 November 2020):1–12.
33. Zambrano H, Anchundia K, Aviles D, Andaluz R, Calderon N, Torres E, et al. Seroprevalence of SARS-CoV-2 immunoglobulins in pregnant women and neonatal cord blood from a highly impacted region. Placenta. 2021;115:146–50. Available from: https://linkinghub.elsevier.com/retrieve/pii/S014340042100610X.
34. Molenaar NM, Rommel A, de Witte L, Dolan SM, Lieb W, Ibroci E, et al. SARS-CoV-2 during pregnancy and associated outcomes: results from an ongoing prospective cohort. Paediatr Perinat Epidemiol. 2022;36(4):466–75. https://doi.org/10.1111/ppe.12812.
35. Sze S, Pan D, Nevill CR, Gray LJ, Martin CA, Nazareth J, et al. Ethnicity and clinical outcomes in COVID-19: A systematic review and meta-analysis. EClinicalMedicine. 2020;29–30:100630. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2589537020303746.
36. Otero S, Miller ES, Sunderraj A, Shanes ED, Sakowicz A, Goldstein JA, et al. Maternal Antibody Response and Transplacental Transfer Following Severe Acute Respiratory Syndrome Coronavirus 2 Infection or Vaccination in Pregnancy. Clin Infect Dis. 2023;76(2):220–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/36348510.
37. Martin-Vicente M, Carrasco I, Muñoz-Gomez MJ, Lobo AH, Mas V, Vigil-Vázquez S, et al. Antibody levels to <scp>SARS-CoV</scp> -2 spike protein in mothers and children from delivery to six months later. Birth. 2022; Available from: https://onlinelibrary.wiley.com/doi/https://doi.org/10.1111/birt.12667.
38. Beharier O, Plitman Mayo R, Raz T, Nahum Sacks K, Schreiber L, Suissa-Cohen Y, et al. Efficient maternal to neonatal transfer of antibodies against SARS-CoV-2 and BNT162b2 mRNA COVID-19 vaccine. J Clin Invest. 2021;131(13). Available from: https://www.jci.org/articles/view/150319.
39. Zelini P, D'Angelo P, Zavaglio F, Soleymaninejadian E, Mariani L, Perotti F, et al. Inflammatory and Immune Responses during SARS-CoV-2 Infection in Vaccinated and Non-Vaccinated Pregnant Women and Their Newborns. Pathogens. 2023;12(5):664. Available from: https://www.mdpi.com/2076-0817/12/5/664.
40. Brebant D, Couffignal C, Manchon P, Duquesne S, Picone O, Vauloup-Fellous C. Transplacental transfer of anti-SARS-CoV-2 neutralizing antibodies in comparison to other pathogens total antibodies. J Clin Virol. 2023;165:105495. Available from: https://linkinghub.elsevier.com/retrieve/pii/S138665322300118X.
41. Palmeira P, Quinello C, Silveira-Lessa AL, Zago CA, Carneiro-Sampaio M. IgG placental transfer in healthy and pathological pregnancies. Clin Dev Immunol. 2012;2012.
42. Edlow AG, Li JZ, Collier ARY, Atyeo C, James KE, Boatin AA, et al. Assessment of Maternal and Neonatal SARS-CoV-2 Viral Load, Transplacental Antibody Transfer, and Placental Pathology in Pregnancies During the COVID-19 Pandemic. JAMA Netw Open. 2020;3(12):e2030455.
43. Joseph NT, Dude CM, Verkerke HP, Irby LS, Dunlop AL, Patel RM, et al. Maternal Antibody Response, Neutralizing Potency, and Placental Antibody Transfer After Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection. Obstet Gynecol. 2021;Publish Ah. Available from: https://journals.lww.com/https://doi.org/10.1097/AOG.0000000000004440.
44. Auriti C, De Rose D, Mondì V, Stolfi I, Tzialla C. Neonatal SARS-CoV-2 Infection: Practical Tips. Pathogens. 2021;10(5):611. Available from: https://www.mdpi.com/2076-0817/10/5/611.

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