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RESEARCH ARTICLE

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SARS-CoV-2 IgG "heritage" in newborn: A credit of maternal natural infection

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Abstract

Description of transplacental passage of specific SARS-CoV-2 IgG from mothers who contracted natural infection to their newborns. Retrospective cohort analysis including pregnant women diagnosed with SARS-CoV-2 and their newborns both tested for SARS-CoV-2 specific IgG and IgM with antibody titration at delivery. Nasopharyngeal swab were taken from both mothers and neonates, and tested for SARS-CoV-2 using polymerase chain reaction (PCR). IgM and IgG were analyzed in maternal and neonatal serum of 143 mother–infant dyads. 86% of women with a positive SARS-CoV-2 PCR >14 days before delivery developed specific IgG and 84% of their infants showed transplacental passage of IgG. Pregnant women infected with SARS-CoV-2 achieve antibody seroconversion following the kinetics described in the general population, and transplacental transfer of IgG specific antibodies occurs. No conclusion can be drawn on passive immunity efficacy or duration.

KEYWORDS
natural infection, passive immunity, SARS-CoV-2

1 | INTRODUCTION

Although the pathogen SARS-CoV-2 is highly contagious, neonates born to women with asymptomatic or symptomatic COVID-19 are rarely infected by the virus.[1] A recent systematic review including a total of 47 studies describing 1188 SARS-CoV-2 positive pregnant women and 985 neonates reported the rate of neonatal infection to be as low as 0.3%.[2]

Vertical transmission of SARS-CoV-2 can occur via different routes: the virus might be transmitted to the fetus through the

placenta,[3] or via vaginal fluids during delivery.[4] In the latter case, SARS-CoV-2 might enter the neonatal nasopharynx during vaginal delivery and potentially trigger neonatal infection when vaginal and rectal swabs of the mothers contain the virus. However, the systematic review published by Walker et al.[5] including data of 655 women and 666 neonates demonstrated that the rate of neonatal infection was no greater when the baby was born vaginally.

Passive immunity might play a key role in protecting newborns of SARS-CoV-2 positive mothers from the infection, similarly to what happens for other infections such as pertussis.[6] Several authors have recently demonstrated the passage of SARS-CoV-2 specific antibodies from vaccinated mothers to their offspring[7] showing that the rate of antibody transfer to the neonate was as high as 100%.[8] Only a few studies have investigated the passage of maternal antibodies to the fetuses[9–16] during natural infection. The data published on this topic describe transplacental IgG passage in a high proportion (almost 90%) of neonates born from SARS-CoV-2 infected mothers.[17,18]

We analyzed the SARS-CoV-2 antibody profile in the infected mothers and their offspring in the largest cohort to our knowledge aiming to investigate passive immunization during SARS-CoV-2 natural infection.

2 | METHODS

A retrospective cohort analysis of mothers with a SARS-CoV-2 positive polymerase chain reaction (PCR) on nasopharyngeal swab (NPS) during pregnancy or at delivery and their newborns was conducted at Santo Stefano Hospital in Prato, Italy, from March 2020 to January 2022. The study was approved by the local Ethical Committee and informed consent was obtained from study participants.

SARS-CoV-2 PCR on NPS were performed as universal screening testing on admission to the delivery unit[19] and in women presenting COVID-19 symptoms.

All positive SARS-CoV-2 pregnant women and their newborns were tested for SARS-CoV-2 Spike-specific IgG and IgM (Access SARS-CoV-2 IgG/IgM; Beckman Coulter) with antibody titration at delivery. The offspring also underwent PCR on NPS at Day 1 of life, to ascertain the presence/absence of SARS-CoV-2 infection.

All NPS were analyzed using STARMag Universal Cartridge kit (Seegene) for RNA extraction and Allplex SARS CoV-2 Assay kit (Seegene) for PCR.

Maternal and neonatal data were extracted from electronic medical records. Data extracted included maternal age, type of delivery (vaginal or cesarean section), gestational age at delivery, presence/absence of SARS-CoV-2 infection symptoms, and their entity (mild—flu-like symptoms, moderate—decreased oxygen saturation and positive imaging, severe—need of intensive care),[20] interval between SARS-CoV-2 positive PCR and delivery, maternal and newborns serologic status, and neonatal PCR.

A previously published case reported from the same hospital, which demonstrated SARS-CoV-2 neonatal passive immunity, was included.[16]

Data were analyzed with descriptive statistics. Quantitative variables were expressed in number and percentages. Mean and standard deviation and medians and ranges (minimum–maximum values) were reported for normally and non-normally distributed data, respectively.

3 | RESULTS

A total of 269 SARS CoV2 positive pregnant women delivered at Santo Stefano Hospital in Prato, Italy, from March 2020 to January 2022. One hundred forty-three mother–infant dyads with complete data on Spike-specific antibodies of IgM and IgG isotypes in maternal and neonatal serum were analyzed. One hundred twenty-six dyads were excluded for incomplete data.

The characteristics of the population studied are reported in Table 1.

Dividing the sample according to the interval between maternal PCR testing and delivery, 13 out of 143 women were found to be SARS-CoV-2 PCR positive at delivery (group 1), 85 cases 1–7 days before the delivery (group 2), 23 cases 8–14 days (group 3), and 22

TABLE 1 Maternal demographic and clinical characteristics

Mothers (*n* = 143)	
Age (years), median (range)	33 (20–43)
Type of delivery	
– Caesarean section	42
– Vaginal delivery	101
Days of SARS-CoV-2 infection before delivery median (range)	4 (0–195)
Asymptomatic	107
Symptomatic	
– Mild	14
– Moderate	19
– Severe	3
Gestational age at delivery (weeks), mean (SD)	39 (±11 days)
Interval between maternal PCR testing and delivery	At delivery: 13 women 1–7 days before delivery: 85 women 8–14 days before delivery: 23 women >14 days before delivery: 22 women

Abbreviations: PCR, polymerase chain reaction; SD, standard deviation.

cases (group 4) more than 14 days before giving birth (maximum 195 days before delivery).

With regard to IgG, in group 1, 3 women (23%) had developed IgG antibodies and 2 newborns (66%) had positive IgG, in group 2, 27 women (31%) had developed IgG antibodies and 22 newborns (81%) had positive IgG, in group 3, 14 women (60%) had developed IgG antibodies and 8 newborns (57%) had positive IgG, finally in group 4, 19 women (86%) had developed IgG antibodies and 16 newborns (84%) had positive IgG. As the interval between maternal SARS-CoV-2 PCR positivity and the delivery increased, the rates of maternal IgG seropositivity also raised (Table 2a).

Five neonates were found to be IgG positive although they were born to IgG negative mothers (1 in the first, second, and third group respectively, and 2 in the fourth) (Table 2b).

As far as IgM is concerned, in group 1, 2 women (15%) had developed IgM antibodies, in group 2, 11 women (13%) had developed IgM antibodies, in group 3, 7 women (30%) had developed IgM antibodies, finally in group 4, 5 women (22%) showed IgM antibodies (Table 2a).

Two newborns had positive IgM antibodies, the first was IgG negative and IgM positive, with a negative PCR and was born to an IgG and IgM negative mother, who was found to be SARS-CoV-2 positive at delivery; the second was both IgG and IgM positive, had a negative PCR and was born to an IgG and IgM positive mother who was diagnosed with symptomatic (fever and dyspnea) COVID-19 14 days before delivery (Table 2b).

As far as PCR neonatal testing is concerned, 10 offspring had positive SARS-CoV-2 PCR with low viral load at Day 1 of life. Eight were IgG and IgM negative and 2 were IgG positive and IgM negative. They were all born at term, 7 vaginally and 2 by C-section. The median interval between diagnosis of maternal infection and delivery was 4 days (min 0–max 14). Seven mothers were IgG and IgM negative and 3 were IgG positive and IgM negative. All newborns were retested 24–48 h later, 9 of them resulted SARS-CoV-2 negative and 1 was confirmed to be SARS-CoV-2 positive (IgG and IgM negative, born vaginally

TABLE 2a Time of maternal infection and evidence of SARS-CoV-2 Spike-specific antibodies in maternal serum

Time of infection (first positive PCR)	No of cases (143)	Maternal serum: IgG	Maternal serum: IgM
Group 1 At delivery	13	Pos: 3	Pos:2
		Neg: 10	Neg: 11
Group 2 1–7 days before delivery	85	Pos: 27	Pos: 11
		Neg: 58	Neg: 74
Group 3 8–14 days before delivery	23	Pos: 14	Pos: 7
		Neg: 9	Neg: 16
Group 4 >14 days before delivery	22	Pos: 19	Pos: 5
		Neg: 3	Neg: 17

Abbreviations: Neg, negative; Pos, postive.

TABLE 2b Time of maternal infection and evidence of SARS-CoV-2 Spike-specific antibodies in neonatal serum

Time of infection (first positive PCR)	No of cases (143)	Neonatal serum: IgG		Neonatal serum: IgM	
Group 1 At delivery	13	Pos: 3	Mothers IgG+: 2	Pos: 1	Mother IgM+: 0
			Mothers IgG−: 1		Mother IgM−: 1
		Neg: 10	Mothers IgG+: 1	Neg: 12	Mothers IgM+: 2
			Mothers IgM−: 9		Mothers IgM−: 10
Group 2 1–7 days before delivery	85	Pos: 23	Mothers IgG+: 22	Pos: 0	
			Mothers IgG−: 1		
		Neg: 62	Mothers IgG+: 5	Neg: 85	Mothers IgM+: 11
			Mothers IgG−: 57		Mothers IgM−: 74
Group 3 8–14 days before delivery	23	Pos: 9	Mothers IgG+: 8	Pos: 1	Mothers IgM+: 1
			Mothers IgG−: 1		Mothers IgM−: 0
		Neg: 14	Mothers IgG+: 6	Neg: 22	Mothers IgM+: 6
			Mothers IgG−: 8		Mothers IgM−: 16
Group 4 >14 days before delivery	22	Pos: 18	Mothers IgG+: 16	Pos: 0	
			Mothers IgG−: 2		
		Neg: 4	Mothers IgG+: 3	Neg: 22	Mothers IgM+: 5
			Mothers IgM−: 1		Mothers IgM−: 17

Abbreviations: Neg, negative; Pos, postive.

TABLE 3 Maternal and neonatal serum SARS-CoV-2 Spike-specific antibodies

Maternal serum, Spike-specific antibodies (*n* = 143)	Neonatal serum, Spike-specific antibodies (*n* = 143)
IgG negative, IgM negative (*n* = 72)	IgG negative, IgM negative (*n* = 68)
	IgG positive, IgM negative (*n* = 3)
	IgG negative, IgM positive (*n* = 1)
IgG negative, IgM positive (*n* = 8)	IgG negative, IgM negative (*n* = 6)
	IgG positive, IgM negative (*n* = 2)
IgG positive, IgM positive (*n* = 17)	IgG positive, IgM negative (*n* = 11)
	IgG negative, IgM negative (*n* = 5)
	IgG positive, IgM positive (*n* = 1)
IgG positive, IgM negative (*n* = 46)	IgG positive, IgM negative (*n* = 36)
	IgG negative, IgM negative (*n* = 10)

from a seronegative asymptomatic mother with positive PCR 2 days before delivery). No newborn showed COVID-19 symptoms.

Table 3 shows the sample divided according to Spike-specific IgG and IgM. IgG and IgM were both negative in 72 mothers (50%), 68 of their infants (94%) resulted IgG and IgM negative. Eight mothers (6%) tested IgM positive and IgG negative, 6 of their newborns (75%) were IgG and IgM negative. In 17 cases (12%), maternal IgG and IgM were both positive, among their infants, 11 (65%) were IgG positive and IgM negative. Forty-six mothers (32%) resulted IgG positive and IgM negative, 36 of their newborns (78%) were found to be IgG positive and IgM negative (Table 3).

4 | DISCUSSION

This study included the largest cohort which has evaluated passive immunity in SARS-CoV-2 positive pregnant women to our knowledge.

Only a few studies, mainly case reports and case series, have investigated the transplacental passage of SARS-CoV-2 specific antibodies in women who have contracted natural infection.

Dong et al.[12] and Zeng et al.[14] first studied the serology of mother–infant dyad in COVID-19, showing the presence of IgG in 6 newborns of SARS-CoV-2 IgG positive women. Fenizia et al.[9] reported 31 SARS-CoV-2 pregnant patients, showing that 63% of the mothers were IgG and 32% IgM positive, respectively, with regard to the newborns, 40% were IgG positive. Milbak et al.[17] studied maternal antibodies in 28 SARS-CoV-2 positive women showing seroconversion in 90% women from 16 days or more after confirmed infection, with regard to umbilical cord blood samples, antibodies were detected in 94% cord blood samples of pregnancies where the woman was seropositive and delivered from day 26 after infection. Flannery et al.[18] detected IgG/IgM SARS-CoV2 antibodies in 83 pregnant women, IgG were detected in cord blood of 72/83 newborns (87%).

In our analysis, the population was divided into four subgroups according to the interval between SARS-CoV-2 infection diagnosis and delivery (and serology collection), showing that rates of maternal IgG seropositivity raised as the interval between maternal infection and the delivery increased. This result is in agreement with previously published data on immunological response in SARS-CoV-2 infection, that demonstrated that specific full immunological response is produced in 7–14 days.[21]

We found that transplacental transfer of IgG was higher in neonates born to mothers with SARS-CoV-2 infection older than 14 days before delivery. This is in line with what previously reported in the paper by Milbak et al.,[17] showing that the longer the interval between infection and delivery, the higher the rate of maternal seroconversion and of antibody transfer to newborns.

IgM specific antibodies were detected in 2 newborns, none of them had positive PCR for SARS-CoV-2 at birth. These findings are in contrast with recognized immunological knowledge, considering that IgM is not usually transferred from mother to fetus because of its larger macromolecular structure. A possible explanation could be the vascular damage associated with SARS-CoV-2, thus the ischemic injury to the placenta could allow the transfer of IgM to the fetus, a mechanism already proposed by Zeng et al.[14] Alternatively, IgM could have been produced by the newborn if the virus crossed the placenta, thus representing possible cases of vertical transmission, although the newborns had a negative PCR and were asymptomatic at birth. Fenizia et al.[9] reported one IgM positive newborn, since in this case the placenta was positive for viral genome and the neonate had a positive PCR on NPS, they considered it suggestive of vertical transmission, despite the newborn didn't show any symptom of COVID-19. Unfortunately in our cohort placental swab were not collected. Anal swab might have been an alternative way to detect the infection in case of transplacental passage of the virus, unfortunately anal swabs were not analyzed in our study as well.

IgG positive newborns from IgG negative mothers might represent cases of vertical transmission as well, although always with negative PCR. Another possible explanation of this finding might

be that IgG waned from the mother in cases of early infection in pregnancy, while still present in neonatal blood after transplacental passage. IgG positive newborns from IgG negative mothers were, however, also present in the subgroups with recently diagnosed SARS-CoV-2 infection. IgG negative neonates from IgG positive mothers might be related to failure of the passage of antibodies with the mechanism proposed by Atyeo et al.[22] and Timi et al.,[23] who postulated that SARS-CoV-2-specific antibody placental transfer is significantly reduced and cord titers and functional activity were lower than in maternal plasma in third-trimester infection due to placental damage.

Several studies are currently available regarding the transplacental passage of specific SARS-CoV-2 antibodies in vaccinated mothers. Trostle et al.[24] reported that specific IgG were present in 100% of the 36 pregnant women included in the study. Similar percentages were also reported by Zdanowski et al.[8] A systematic review conducted by Falsaperla et al.[25] including 7 studies for a total of 351 women showed that 95.2% of maternal sera were positive to anti-SARS-CoV-2 antibodies as well as 85% of umbilical cord blood samples. Fu et al.[26] showed similar data and demonstrated increasing placental transfer ratios in cord blood associated with increasing time from the first vaccine dose to delivery, suggesting there might be an optimal timing of vaccination in pregnancy to confer passive immunity to the newborn. Kashani-Ligumsky et al.[27] also reported this phenomenon: they compared the SARS-CoV2 serology of cord blood of vaccinated mothers and of women who contracted natural infections, showing higher antibody titers among women who had received the vaccine. The reason for reduced rates of seroconversion and antibody transplacental passage in natural infection with respect to vaccination is yet to be ascertained.

With regard to the 10 asymptomatic neonates found positive at PCR on NPS immediately after birth, only one of these newborns was found positive at PCR on confirmatory NPS. This neonate might represent a possible case of vertical transmission (vaginal birth from a seronegative mother with positive PCR 2 days before delivery, with neither IgG nor IgM detected in the newborn). A possible explanation of the 9 negative result at the confirmatory NPS might be that the low amount of viral RNA had entered the nasopharynx without triggering neonatal infection, passive immunity might have contributed since 2 neonates were IgG positive.

5 | CONCLUSIONS

Our data underline that pregnant women positive for SARS-CoV2 achieve antibody seroconversion following the kinetics described in the general population. Transplacental transfer of IgG specific antibodies occurs and specific SARS-CoV-2 IgG are demonstrated in neonates born from affected pregnant women. This is the largest cohort reporting passive immunity in newborns after natural maternal infection with the novel coronavirus, SARS-CoV-2, to our knowledge.

Further studies are needed to analyze how long infants maintain IgG acquired from the mothers and the efficacy in protection from the infection both after natural infection and maternal vaccination.

AUTHOR CONTRIBUTIONS

Conceptualization: Anna Franca Cavaliere, Gianluca Straface, Pier Luigi Vasarri, Ismaele Fusco, Fabrizio Signore, Gianluca Straface, and Monica Gardelli. *Data curation*: Laura Marchi, Annalisa Vidiri, Emanuele Arturo Fera, Marta Pallottini, Federica Perelli, Tamara Brunelli, Paolo Dal Poggetto, and Elena Martelli. *Writing–original draft preparation*: Laura Marchi, Annalisa Vidiri, Emanuele Arturo Fera, and Marta Pallottini. *Writing–review and editing*: Anna Franca Cavaliere, Laura Marchi, and Federica Perelli. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The study was approved by the local Ethical Committee (51-21 PO) and informed consent was obtained by study participants.

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