Maternal SARS-CoV-2 IgG provides limited protection for their infants

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Abstract

At present, there are still many ambiguous reports about the perinatal infection of infants born to mothers infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1-3]. The dynamic characteristics of infantile serum antibodies born to mother with SARS-CoV-2 has not been well described[4-6]. In this study, we analyzed the seroconversion of 27 newborns born to 26 pregnant women infected with SARS-CoV-2. The SARS-CoV-2 IgG positive rate of parturients was 80.8%, and half of their infants obtained maternal IgG. IgG transfer rates were 18.8% and 81.8% in those infants whose mother infected less and more than 2 weeks before delivery respectively. In the first two months of life, the IgG level of infants dropped sharply to one tenth of that at birth. The IgM was confirmed positive in 53.8% of mothers and negative in all infants. These results suggest that maternal IgG has limited protection for infants, which may help us to improve vaccination strategies in future.

Introduction

Pregnant women seem to be more vulnerable to coronavirus infected disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection due to the characteristic immune responses during pregnancy. It has been found that more than 13% admitted pregnant women were symptomatically with SARS-CoV-2 infection[9]. Vertical transmission of SARS-CoV-2 has not yet been detected, whereas perinatal transmission has been suspected in a few cases[10-12]. Due to the limitations of viral nucleic acid detection, SARS-CoV-2 serological antibody's detection plays an important role in the diagnosis of pregnant women and their newborns[13].

It is well known that when a woman was infected with a particular virus during pregnancy, the fetus can obtain specific maternal IgG through placental transport, which plays a passive immune role to protect the baby from virus infection after birth[13]. Changes of the level of baby's specific antibodies can also prompt the intrauterine exposure risk. While the maternal gestational age (GA) at infected time and the duration of infection before delivery may affect their babies' seroconversion. The dynamic changes of antibodies against SARS-CoV-2 were different from those of ordinary respiratory viruses[16-18]. The acquisition, maintenance time and protective effect of maternal antibody in infants are still unclear[19]. Here, we described the serodynamic results of pregnant women with SARS-CoV-2 infection and their infants delivered in Zhongnan Hospital of Wuhan University in Wuhan, China.

Results

Objects and characteristics. Between January 27, 2020 and May 10, 2020, 26 pregnant women were confirmed to be infected with SARS-CoV-2 by laboratory evidences, and their 27 babies were tested for IgM and IgG antibodies against SARS-CoV-2 by chemiluminescence method. The positive rate of viral pneumonia-like in computed tomography (CT), SARS-CoV-2 seroconversion and viral nucleic acid test

were 88.4% (23/26), 80.8% (21/26) and 34.6% (9/26) respectively in parturient women, while all infants were negative in SARS-CoV-2 nucleic acid test at birth. The age range of the mothers was 22-41 years, and the range of gestational age at admission was 31^{+6} to 41^{+1} weeks. There were 5 pregnant women with SARS-CoV-2 infection in the second trimester and 21 cases infected in the third pregnancy. 13 pregnant women had COVID-19-like symptoms such as fever and/or cough before delivery. Of the 27 infants, 21 were full-term, the other 6 were preterm including 1 pair of twins. The infants were normal at birth with Apgar scores all over 7. All infants were separated from their mothers immediately and were not breastfed before SARS-CoV-2 antibodies testing. The median time from onset of SARS-CoV-2 infection to delivery of parturients women was 10.5 days (1-107 days), and the primary seroconversion of IgG and IgM were 80.8% (21/26) and 53.9% (14/26) respectively. (Table 1).

Detection and seroconversion of mothers and infants. Wuhan was the epicenter of SARS-CoV-2 outbreak, and from February to June in 2020, all parturient women need to undergo the throat swab SARS-CoV-2 polymerase chain reaction with reverse transcription (RT-PCR) detection and lung CT examination before delivery. Since serological testing had not been widely used until March 2020, serum SARS-CoV-2 antibody detection was carried out in two stages: mothers who delivered before March 2020 received antibody testing in the follow-up stage after delivery, and pregnant women who gave birth after March 2020 were detected antibody before delivery.

Eleven pregnant women underwent serological testing 1-8 days before delivery. During pregnancy, they had positive of SARS-CoV-2 nucleic acid test or lung CT examination that showed lung viral pneumonia-like changes. The median time from infection to delivery was 70 days (6-107 days), and the median time from infection to antibody detection was 69 days (16-99 days). All those mothers were IgG positive (11/11, 100%), 63.6% cases were IgM positive (7/11). The IgG was positive in 9 (9/11, 81.8%) infants born to this group mothers. Fifteen mothers who were confirmed with SARS-CoV-2 infection before delivery with symptoms, or without symptoms but with lung viral pneumonia-like changes, underwent antibodies test after delivery. The median time from infection to delivery was 4.5 days (1-15 days), and the median time from infection to antibody detection was 64.5 days (36-81 days). Among this group of mothers, 40% (6/15) were IgM positive, and 66.7% (10/15) were IgG positive. Of their 16 infants, only 2 cases (12.5%, 2/16) were IgG positive. From these results, we speculate that maternal SARS-CoV-2 seroconversion rate was related to the infection duration of pregnant women before delivery.

Of 21 serum positive mothers, 53.8% (14 /21) cases were both IgG and IgM positive, there were 26.9% cases (7/21) with single IgG positive and no single IgM positive case. 12 infants (12/27, 44.4%) were IgG positive, and none of them was IgM positive. Five mothers infected in the second trimester were all IgG positive, while their babies with 60% IgG positive rate. Among 21 mothers infected in the third trimester, 17 (81.0%) were IgG positive, and 9 infants (40.9%) were IgG positive (Table 1). Of the 22 infants born to 21 IgG-positive mothers, only 11 (50.0%) were IgG positive.We found that only half of infants obtained maternal IgG from SARS-CoV-2 infected mothers, regardless of the gestational age at which the mothers were infected.

Factors related to infantile acquisition of maternal IgG. To further understand the serodynamic changes of IgG and IgM in mothers and infants, we compared the correlation between maternal antibody level and infant serum conversion. As shown in figure 1a and 1b, there was no correlation between duration of maternal infection time and the titer of serum IgM and IgG . Because all detection was performed 16 days after maternal infection, these results implied that although the IgM titer indicated a downward trend, maternal IgG and IgM rose rapidly to high levels during the observation period and maintained at a platform stage. And the levels of IgG were positive correlated to that of IgM (p=0.0035) (Figure 1c). We also compared the correlation of the maternal serum antibodies titer with that of their infants, and found that the serum IgG titer of infants was positive correlated to that their mothers (p=0.01)(Figure 1d). These data demonstrated that infants could acquired more IgG from those mothers with higher titer of serum IgG. A similar rule was found in the positive correlation between the serum antibody level of infants and the time of infection of mothers before delivery (Figure 1d).

According to the time from onset of SARS-CoV-2 infection to delivery of mothers, we divided this group of data into 2 groups which were within 14-day and more than 14-day. The IgG seroconversion rates of mothers were 66.7% (10/15) and 100% (11/11), while the infants' IgG positive rates were 18.8% (3/16) and 81.8% (9/11), respectively (p value=0.002). Then we analyzed the relationship between the maternal and infantile IgG antibody titers and found that the two showed a positive correlation (Figure 1e). The maternal IgG antibody titer was used to predict the positive of infantile IgG after birth (>1s/co), with a cutoff value of 8.22 s/co, which had a sensitivity of 84.3% and a specificity of 93.3% (Figure 1f).

Effects of mothers with and without symptoms on IgG conversion in infants. It has been suggested that asymptomatic individuals had a weaker immune response to SARS-CoV-2 infection in non-pregnant population[20]. The seroconversion rate of mothers with symptoms before delivery was significantly higher than that of mothers without symptoms, and the IgM seroconversion rate of asymptomatic mothers was lower. However, there was no significant difference of IgG and IgM titer between these two groups of data (Table 2). The dynamic characteristics of maternal IgG and IgM titer against SARS-CoV-2 of those with and without symptoms were consistent with reported above. While whether mothers had symptoms did not affect the IgG conversion rate of their infants.

Serodynamic characteristics of maternal IgG. In this study, four mothers were performed twice quantification tests of serum antibodies (Figure 2a). They all had symptoms of fever or cough at the beginning of the onset with typical COVID-19 pneumonia findings of chest CT images. The median interval time between detection and onset of two tests were 26.5 days (17-46 days) and 72 days (62-91 days). The average serum titer of IgG was 11.1 s/co and 8.3 s/co, and the average titer of IgM was 8.5 s/co and 13.6 s/co respectively. The antibodies were also detected twice in their 4 infants on the first day and the day of 31-63 after birth (Figure 2b). The IgM levels of all infants were below threshold, and the average IgG levels were 9.2 s/co and 1.0 s/co respectively. Infantile IgG levels decreased sharply in the first two months of life, accounting for only 10.7% of the titer at birth. These results show that after two to three months of infection with SARS-CoV-2, the IgM levers of these 4 mothers with COVID-19 gradually increased while most IgG (3/4, 75.0%) showed a downward trend. This is not on par with the dynamic

regularity of antibodies in other viral infection. Many similar results have reported that the serum antibodies dynamic of this novel virus surprised all of us[17,21-23].We also found that without breast feeding, the maternal protective effect in infants was rapidly eliminated naturally within two months after birth (Table 3). It is worth noting that this rate of decline was beyond expectations.

Discussion

In this study, we report antibody responses to SARS-CoV-2 in 26 pregnant women with COVID-19 and the seroconversion of their 27 babies. The probability of infantile acquisition of maternal antibody was related to the infection time before delivery and the serum antibody concentration of their mothers. The cutoff value was 8.22 s/co in mother, which had a sensitivity of 84.3% and a specificity of 93.3% for predicting postnatal infantile IgG positive (>1 s/co). In the first two months of life, the IgG level of infants dropped sharply, only one tenth of that at birth. The IgM positive rate was 53.8% in mothers and negative in all infants. These results imply that maternal IgG provided limited protection for their infants, which may be helpful to improve vaccination strategy in the future.

The impacts of maternal SARS-CoV-2 infection on the fetus may include vertical transmission, abnormal intrauterine growth, abortion and stillbirth[3,24-26]. Due to the role of placental barrier, maternal SARS-CoV-2 IgG in infants can be used to observe whether they has acquired the passive immunity, while the increase of fetal IgM can be used to judge whether there is intrauterine exposure. At present, there are few studies focusing on serodynamics of infants born to mothers with SARS-CoV-2 infection during postpartum period. Different from previous case reports, our data show that no positive results of IgM were found in infants born to mothers with SARS-CoV-2, regardless of the mother's clinical symptoms, antibody titer and infection during the second or third trimester[1,5]. These results were further supported by polymerase chain reaction with reverse transcription (RT-PCR) detection of throat swabs, suggesting that the probability of intrauterine vertical transmission caused by maternal infection of SAR-CoV-2 during pregnancy is very rare in non critical cases[6].

There are many factors that affect infants to obtain maternal passive immunity. Despite the abundance of antibodies produced by prenatal infection of mothers, infants did not obtain the IgG titer in proportion to their mothers due to the short time period between maternal infection and delivery. This is consistent with our expectations, in which the longer the mother infected the virus before delivery, the higher the seroconversion rate of the maternal IgG, and the greater the probability of infants obtaining maternal antibody.

Mothers who had been infected for more than two weeks give their babies more adequate antibody titers. However, the longer the intrauterine exposure was, the more likely it was to affect the development of the fetus, which constitutes other high-risk factors[6]. The maternal IgG transfer efficiency was also depended on the mother's immune response to SARS-CoV-2. The IgG titer of infants born to high titer IgG mothers also increased. The duration of effective concentration of maternal SARS-CoV-2 IgG in infants is related to vaccination procedures for infants and their risk of infection after birth. It is generally believed that

maternal antibodies disappear gradually in 12-18 months after birth. However, the maternal protective effect of against SARS-CoV-2 in infants was rapidly eliminated naturally after birth. These results can help us understand the risk of infantile vulnerability and improve vaccination procedures in the future[27,28]. Based on the fact that the titer of maternal antibody in infants' serum decreased faster than expected, we believe that it may be an appropriate time to vaccinate a safe and reliable SARS-CoV-2 vaccination in 2 months after birth.

In summary, the infection time and antibody titer of mothers before delivery affected the effect of infants obtaining maternal IgG, and the passive immunity lasted for a short time and disappeared in 2 months after birth. Our study has some limitations. This study is a retrospective study and no comparison was made between the antibody titer of the mother before delivery and the antibody titer of the baby at birth. And whether the specific antibody in the baby can play a protective effect needs further observation, and more data are needed for the following studies.

Declarations

Conflict of interest statement: No conflict of interest.

Author Contributions: X Wang, P Yang, J Zheng, P Liu and D Zhao conceptualized the study design. X Wang, P Yang, C Wei, Y Zhang and J Guo recruited the patients, collected specimens, collected demographic, clinical, and laboratory data; X Wang, J Zheng, P Liu and P Yang interpreted the laboratory result; P Liu, J Zheng, Y Zhang and D Zhao analyzed the data; and X Wang, P Yang, J Zheng and D Zhao wrote the initial drafts of the manuscript; All authors read and approved the final report and have no conflicting issues with the contributions listed herein.

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Ethics statement: The protocol and procedures employed were reviewed and approved by the appropriate institutional review committee and followed the principles outlined in the Helsinki Declaration.

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Methods

1. **Objective**. In this paper, the serum antibodies of 26 pregnant women who were diagnosed with SARS-CoV-2 infection and 27 infants (1 pair of twins) in Zhongnan Hospital of Wuhan University from January 27, 2020 to May 10, 2020 were analyzed. The infants were admitted to neonatology department for serological antibody test after birth. The mother began breastfeeding if they were asynptomatic after 2 weeks of isolation and negative result of viral nucleic acid detection. During the follow-up with 3 months after the birth of the infant, the results of serum antibody test of SARS-CoV-2 in 4 mothers and 4 infants were obtained.
2. **Diagnosis of pregnant women SARS-Cov-2 infection**. According to the supply of detection kit, maternal antibody detection was divided into two stages. Wuhan was the epidemic center of SARS-CoV-2, all pregnant women suspected with SARS-CoV-2 infection would be examined the viral RNA by polymerase chain reaction with reverse transcription (RT-PCR) before delivery. Since the serological test had not be widely used until March 2020, the primary time of SARS-CoV-2 antibody detection was performed as: 11 cases were tested for antibody 1-8 days before delivery. They were confirmed to have nucleic acid or lung CT positive during pregnancy. The time from infection to delivery was 70 days (6-107 days), and the median time from infection to antibody detection was 69 days (16-99 days). After delivery, 15 mothers underwent antibody test, but the infection was confirmed before delivery (with or without symptoms, but lung CT was positive). The time from infection to delivery was 4.5 days (1-15 days), and the median time from infection to antibody detection was 64.5 days (36-81 days). In the seventh edition of the guidelines, serological test results were used as the basis for etiological diagnosis.
3. **Detection of serum IgM and IgG antibodies**.The serum IgM and IgG levels were quantified by Axceed 400t automatic chemiluminescent immunoanalyzer (Tianjin boassi Biotechnology Co., Ltd. China) and matching reagents.The test was carried out according to the operating instructions of the kit

(chemiluminescence method). The test result ≥0s/co was defined as positive.3.Detection of SARS-CoV-2 (ORF1ab/N gene) nucleic acid. The SARS-CoV-2 nucleic acid was tested by 2019 novel coronavirus (ORF1ab/N gene) nucleic acid detection kit (BioGerm Medical Technology Company, Shanghai, China) according to the guidelines Chinese Center for Disease Control and prevention.

4. **Definition of SARS-CoV-2 infection in mothers**: Either positive results of nucleic acid or specific antibodies to SARS-CoV-2 detection.
5. **Statistics**.Statistical analyses were performed using a two-tailed unpaired t-test, Fisher's test. P value <0.05 was considered significant. All statistical calculations were performed with Prism 8 (GraphPad Software Inc., La Jolla, CA).
6. **Ethical approval and informed consent:** This study was registered as a clinical study with the Chinese Clinical Trial Registry (ChiCTR-ORC-16008872), and the Medical Ethical Committee of Zhongnan Hospital of Wuhan University approved the study (approval no. 2015019). Informed consent was signed and obtained from all subjects (pregnant women and guardians). The protocol and procedures employed were followed the principles outlined in the Helsinki Declaration.

Tables

Table 1. Clinical data of mothers and infants recruited.

	Infants(n=27)	Mothers(n=26)	P value
Sex			
Male,n(%)	12(44.4)	/	
Female,n(%)	15(57.7)	/	
Median GA,weeks(range)	38.6(31^{+6}~41^{+1})	/	
< 37w,n(%)	6(22.2)	/	
≥ 37w,n(%)	21(80.8)	/	
Median birth weight,g(range)	2880(1490~3850)	/	
< 2500g,n(%)	7(25.9)	/	
≥ 2500g,n(%)	20(74.1)	/	
Apgar score <7 at 1,5min,n(%)	0(0),0(0)	/	
Delivery mode			
Eutocia,n(%)	4(14.8)	4(15.4)	
Cesarean,n(%)	23(85.2)	22(84.6)	
Median age,years(range)	/	31(22~41)	
With symptom of COVID-19,n(%)	0(0)	13(50.0)	
CT scan with viral pneumonia,n(%)	0(0)	23(88.4)	
SARS-CoV-2 nucleic acid(+),n(%)	0(0)	9(34.6)	
GAO			
<28w	/	5(19.2)	
≥28w	/	21(80.8)	
Anti-SARS-CoV-2 IgG and IgM			
IgM(-)/IgG (-),n(%)	15(55.6)	5(19.2)	0.0103
IgM (+)/IgG (-),n/N(%)	0(0)	0(0)	
IgM (-)/IgG (+),n/N(%)	12(44.4)	7(26.9)	0.2492
IgM (+)/IgG (+),n/N(%)	0(0)	14(53.8)	<0.0001
Total IgM (+)	0(0)	14(53.8)	<0.0001
Total IgG (+)	12(44.4)	21(80.8)	0.0244
IgG positive rate(%)			

DMOD≤14d,n/N(%)	3/16(18.8)*,	10/15(66.7)	0.0113
DMOD>14d,n/N(%)	9/11(81.8)**	11/11(100)	0.4762
GAO<28w,n/N(%)	3/5(60.0)	5/5(100)	0.4444
GAO≥28w,n/N(%)	9/22(40.9)	16/21(76.2)	0.0305

Between * and **, p value=0.002. n/N,number of positive or negative cases/number of test cases; CT, computed tomography; DMOD, days of maternal onset to delivery; GAO,gestational age at onset; GA,gestational age.

Table 2. Clinical characteristics of SARS-CoV-2 infected mothers with or without symptoms

	With symptoms (13)	Asymptomatic (13)	P value
Mothers			
Median age,years(range)	31(27~36)	30(22~41)	0.4828
CT scan with viral pneumonia,n(%)	13(100)	10(76.9)	0.22
SARS-CoV-2 nucleic acid(+),n(%)	6(46.2)	3(23.1)	0.411
DMOD,days(range)	12(1~107)	6(3~84)	0.9492
Results of anti-SARS-CoV-2 Abs			
IgM(-)/IgG (-),n(%)	0(0)	5(38.5)	0.008
IgM (+)/IgG (-),n/N(%)	0(0)	0(0)	
IgM (-)/IgG (+),n/N(%)	3(23.1)	4(30.8)	
IgM (+)/IgG (+),n/N(%)	10(76.9)	4(30.8)	
Total IgM (+)	10(76.9)	4(30.8)	0.0472
IgM titer (s/co)	4.79 ± 1.71	3.5 ± 2.30	0.6526
Total IgG (+)	13(100)	8(61.5)	0.0391
IgG titer (s/co)	10.84 ± 3.07	7.39 ± 3.17	0.4414
IgG conversion rate of infants,n/N(%)	7/14(50.0)	5/13(38.5)	0.7036

DMOD,days of maternal onset to delivery. CT, computed tomography.

Table 3. Detailed follow-up data of 4 mothers and 4 infants.

	case1	case2	case3	case4
Date of COVID-19 onset	20th Jan	31th Jan	15th Feb	8th Feb
GA at onset of COVID-19(weeks)	36^{+5}	37^{+1}	35^{+5}	28^{+2}
Date of delivery	16th Feb	16th Feb	3rd Mar	5th Mar
GA at delivery(weeks)	37^{+4}	39^{+3}	38^{+2}	32
Date of 1st Ab detection	16th Feb	16th Feb	3rd Mar	5th Mar
Delivery mode	Cesarean	Cesarean	Cesarean	Cesarean
Maternal 1st IgM(s/co)	1.56	23.6	0.56	8.4
Maternal 1st IgG(s/co)	7.01	11.74	12.06	13.67
Infantile 1st IgM(s/co)	0.1	0.15	0.38	0.2
Infantile 1st IgG(s/co)	5.14	11.39	7.55	12.55
Date of 2nd Ab detection	19th Apr	19th Apr	19th Apr	21th Apr
Days between 1st to 2nd Ab detection(days)	63	63	47	47
Maternal 2nd IgM(s/co)	6.38	34.51	1.48	21.11
Maternal 2nd IgG(s/co)	1.92	15.93	6.18	9.25
Infantile 2nd IgM(s/co)	0.07	0.08	0.06	0.15
Infantile 2nd IgG(s/co)	0.5	1.21	1.01	1.2
Infantile 1st IgG/Maternal 1st IgG(%)	73.32%	97.02%	62.60%	91.81%
Infantile 2nd IgG/Maternal 2nd IgG(%)	26.04%	7.60%	16.34%	12.97%

GA, gestational age; Ab, antibody.

Figures

Figure 1

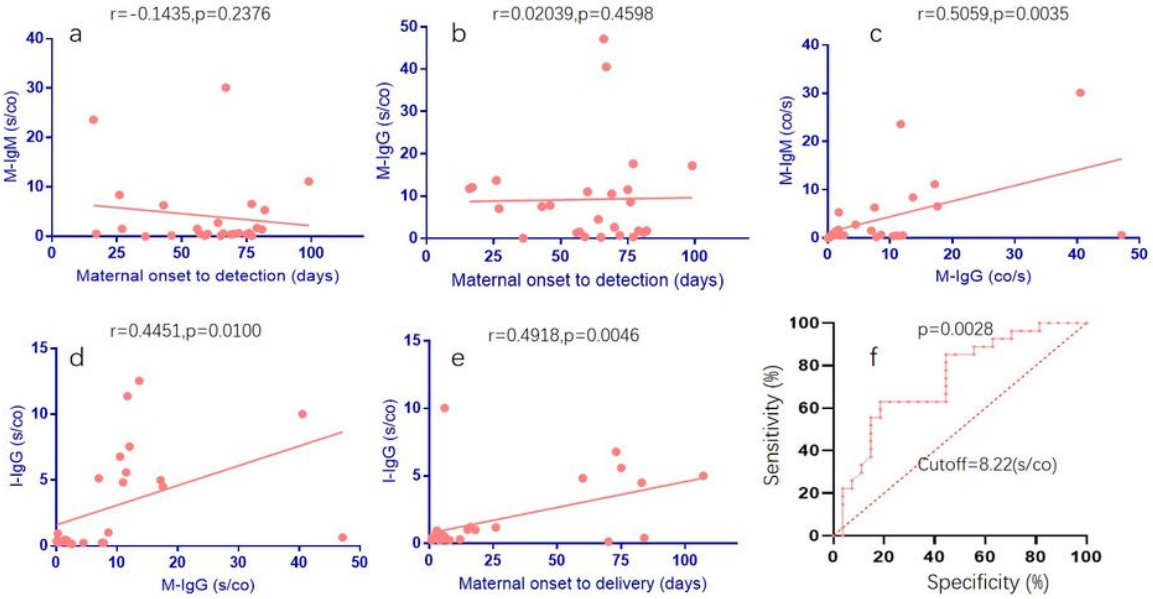

Figure 1

Dynamic characteristics of serum antibodies in pregnant women and infants. 1a, correlation between maternal infection time and serum IgM titer in pregnant women (M-IgM); 1b, correlation between maternal infection time and serum IgG titer in pregnant women (M-IgG); 1c, correlation between the maternal serum IgG and IgM titer in pregnant women; 1d, correlation between maternal serum IgG and infant IgG titer (I-IgG); 1e,correlation between the maternal infection time before delivery and the IgG titer of infants; 1f, predicting the sensitivity and specificity of maternal antibodies transferring into infants. Pearson test was used to analyze the correlation between the two groups, $P < 0.05$ was considered to be statistically significant.

Figure 2

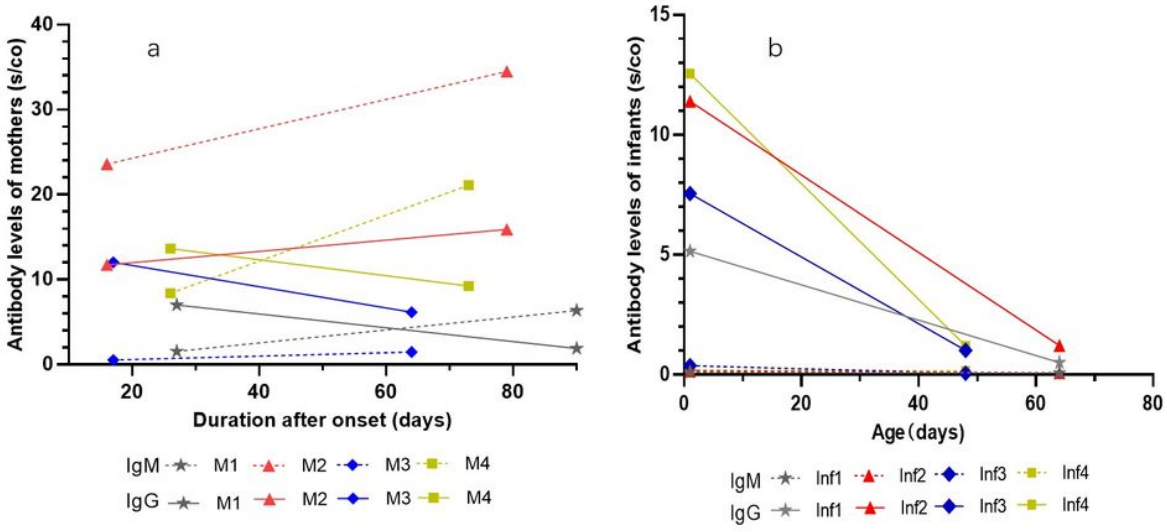

Figure 2

Dynamic changes of serum antibodies to SARS-CoV-2 in 4 COVID-19 mothers and their 4 infants. Antibody concentration ≥1.0s/ Co was defined as positive. Solid lines mean levels of IgG, dotted lines mean levels of IgM. M, cases of mothers; Inf, cases of infants. a, antibodies levels of mothers; the serum antibodies detection interval of mother 1 was on the day of 27 and 91, mother 2 on the day of 16 and 71, mother 3 on the day of 17 and 64, and mother 4 on the day of 26 and 73 after onset. b, antibodies levels of infants; the serum antibodies detection interval of four infants was on the day at birth and the day of 63, 63, 46 and 31 after birth, the same day with their mothers respectively. All 4 infants were formula fed.