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Original Article

SARS-COV-2 IgG antibody response in pregnant women at delivery

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ABSTRACT

Background: The prevalence of COVID-19 infection during pregnancy is not known. COVIPREG is a prospective French multicenter study to assess the seroprevalence at the time of delivery and the maternal and neonatal impact of COVID-19 infection during pregnancy. In order to study factors associated with poor outcomes after COVID-19 Infection during pregnancy and adapt the sample size of the study, a preliminary assessment of the prevalence of SARS-CoV-2 IgG was planned after 500 inclusions in a one perinatal center of Paris area.
Objectives: To assess the prevalence of SARS-CoV-2 IgG antibody response in pregnant women at the time of delivery during the COVID-19 pandemia.
Study design: A prospective observational study at Cochin hospital (Level III maternity). Patients admitted for delivery were offered to participate to the study. Each patient participating to the study was tested for anti-SARS-CoV-2-IgG antibodies using a commercially available ELISA.
Results: Among the 529 patients included in the COVIPREG study between April 29 and June 26, 529 were assessed for SARS-CoV-2 IgG antibody response and 25 had a positive test, ie 4.7 % with a confidence interval at 95 % [3.0 %–6.9 %]).
Conclusions: Four months after the beginning of the infection in Paris, the seroprevalence of SARS-CoV-2 IgG in pregnant women at the time of delivery is low. Studies evaluating the impact of COVID-19 infection during pregnancy should take this information in account in order to adapt the sample size.

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1. Introduction

SARS-CoV-2 is an emerging human coronavirus responsible for the disease called COVID-19 [1]. These viruses are responsible for infections of the respiratory tract, gastrointestinal system and nervous system [1,2]. Human-to-human transmission occurs mainly directly, by the respiratory route or indirectly via aerosols. Manual indirect transmission is possible. Contagiousness precedes symptoms [4]. The incubation period is around 5 days (between 2 and 14 days) [4].

Following the rapid spread of SARS-CoV-2 since December 2019, and in view of the severity of the infection, the WHO declared COVID-19 as a global public health emergency on January 30, 2020 and as a global pandemic from March 11, 2020. By September 15th, there were more than 29 million infections worldwide and over 930,000 deaths. The majority of people infected with SARS-CoV-2 are asymptomatic or present mild symptoms of rhinitis, cough, fever and dyspnea [2]. Digestive signs, anosmia, agueusia may also be present. However, more severe symptoms have been described as pneumonia or acute respiratory distress syndrome (ARDS) [3]. The overall estimate of the mortality rate (including asymptomatic and symptomatic people) seems to be around 5 % [5].

In pregnant women, the symptoms appear to be the same as those in the general population. During the third trimester patients are considered to be at risk of more severe symptoms such as pneumonia or ARDS like other at-risk populations [6,7]. Concerning the risks for the fetus and the newborn very limited information is available at the moment. Fetal infection after transplacental passage of the virus has been described but appears to be very rare [8]. Neonatal infection is rare, and the majority of these infected newborns are asymptomatic even if few severe cases were described [9].

The antibody response after SARS-CoV-2 infection has recently been described. In symptomatic patients, antibodies against SARS-CoV-2 have been reported to be detected from a few days to 3 weeks after onset of symptoms [10,11], with the median of 6 days [12]. High levels of neutralizing antibodies are induced about 10 days after onset of the disease [13]. The presence of SARS-CoV-2 IgG antibodies is indicative of current or previous infection by SARS-CoV-2, however the extent and duration of protection conferred by SARS-CoV-2 IgG antibodies remain unknown [12,14].

The COVIPREG study was designed to study the COVID-19 seroprevalence in pregnant women at the time of delivery, the consequences of the infection for the women and their newborns and the risk factors of severe disease (NCT04355234). It is a prospective study conducted in 10 perinatal centers of Paris area in France. Since no data was available regarding COVID-19 seroprevalence in pregnant women, a preliminary analysis was planned in the study protocol after 500 inclusions in order to adjust the sample size of the study to achieve the objectives. We present the results of this intermediate analysis.

2. Methods

2.1. Patients populations

One perinatal center of Paris area, Cochin Hospital (Port-Royal Maternity, Paris, France) was considered for this preliminary analysis. Pregnant women were prospectively included in the study at the time of delivery between April 29, 2020 and June 26, 2020. All patients admitted to the delivery ward after 15 weeks of gestation (WG) were offered the possibility to participate to the study independently of the gestational age and pregnancy complications. Patients were not referred to our center specifically for COVID-19.

Exclusion criteria were age<18 years, refusal to participate to the study, patient unable to read or understand the study documents. After informed consent of the patient maternal blood was collected and serum samples were stored at −20 °C for COVID-19 Elisa. All data (clinical, laboratory, ultrasonographic) for the mother and the newborns were prospectively collected.

The COVIPREG study was approved by an institutional review board, CPP SUD MEDITERRANEE (N° 2020-A00924-35) on April 23, 2020.

2.2. Serology testing for SARS-CoV-2 specific IgG

Serum samples were tested using the SARS-CoV-2 IgG Architect assay (Abbott, Sligo, Ireland) according to the manufacturer's instructions. The SARS-CoV-2 IgG assay is a chemiluminescent microparticle immunoassay (CMIA) used for the qualitative detection of IgG antibodies to SARS-CoV-2 in human serum and plasma. The resulting chemiluminescent reaction was measured as a relative light unit (RLU). The presence or absence of IgG antibodies to SARS-CoV-2 in the sample (S) is determined by comparing the chemiluminescent RLU in the reaction to the calibrator RLU (C) and expressed as the S/C index. The results were considered negative if the IgG index was < 1.4, positive if ≥1.4. This commercial chemiluminescent immunoassay is validated for clinical use by the FDA with high analytical and clinical performances [15,16].

2.3. Data analysis

Statistical analysis was performed by a dedicated statistician using the SAS 9.4 software.

The main objective of this preliminary analysis was to estimate the seroprevalence of COVID 19 infection and its 95 % confidence interval in the selected sample.

We analyzed maternal characteristics (age, BMI, geographical origin, multiple pregnancy) and the outcome of the pregnancy (term of delivery, mode of delivery and vital status of the child) in positive and negative women. The distribution parameters were mean and standard deviation for quantitative data or number and frequency for qualitative data. For these comparisons, the appropriate tests will be used: Khi-2 or Fisher test.

3. Results

During the study period 529 patients were included in the study and were offered a SARS-CoV-2 IgG testing. Among those, 25 had a positive serology, ie 4.7 % with a confidence interval at 95 % [3.0 %–6.7 %]. None of the patients had symptoms of COVID-19 infection at the time of inclusion. The characteristics of the patients are

Table 1
Maternal and neonatal characteristics of the 529 patients.

	Pregnant women at the time of delivery N = 529
Maternal age	33.7 (4.7)
BMI	22.4 (3.7)
Multiple pregnancy	16 (3.0 %)
SARS-CoV-2 RT PCR during pregnancy	21 (4 %)
Positive SARS-CoV-2 RT PCR during pregnancy	10/21 (47.6 %)
Gestational age at delivery	38.9 (3.3)
Preterm delivery	41 (7.7 %)
Cesarean section rate	81 (15.3 %)
Newborn status	
-Alive	517 (97.7%)
-Stillbirth	12 (2.3 %)

Data shown as mean (standard deviation) or number (%).

summarized in Table 1. Mean maternal age was 33.7 (+/− 4.8) and mean gestational age at delivery was 38.9 (+/− 3.3). Forty-one patients delivered preterm (7.7 %). There were 12 fetal losses, 9 were termination of pregnancy for genetic abnormalities or fetal malformations and 3 were stillbirths (Table 2). These patients were pregnant during peak of COVID-19 outbreak in Paris.

Twenty-one patients had a SARS-CoV-2 RT-PCR test during pregnancy because of COVID-19 symptoms. The SARS-CoV-2 RT-PCR was negative for 11, and all these patients had a negative serology at delivery. The SARS-CoV-2 RT-PCR was positive for 10 and 8 patients had a positive serology whereas 2 had a negative serology at delivery. For one of these 2 patients the IgG index was in the grey zone at 0.8 (grey zone between 0.8 and 1.4 according to the manufacturer). This patient had symptoms of COVID 19 (anosmia) and a positive PCR test two months before delivery. The second patient had a PCR test in a private lab because of moderate fever (37.8 °C) without any other symptom. The PCR test was not checked in our hospital. The IgG index was at 0.0.

One of the patients with a positive serology had a termination of pregnancy at 17 WG for severe fetal malformation (ventriculomegaly, spine malformation and cleft feet) without abnormalities found at the genetic tests. SARS-CoV-2 PCR was negative on fetal tissues.

Maternal and neonatal characteristics were compared between the two groups of patients with positive and negative SARS-CoV-2 serology. No significant difference was found between the two groups concerning maternal age, maternal BMI, geographic origin, twin pregnancy, prematurity rate, mode of delivery nor the rate of fetal loss (Table 3).

4. Discussion

France is a country that was severely touched by COVID-19 outbreak in the first trimester of 2020. First cases were reported in France on January 24th, 2020 and general lockdown was declared by the French government for two months between March 17th and May 11th. At the present time, September 15, France totalizes 381,500 cases and 30,900 deaths due to COVID-19 infection. The study was performed in the Paris area which was particularly affected by the disease and totalized 40 % of national deaths.

The current study shows that, three months after the first cases of COVID-19 infection, seroprevalence of SARS-CoV-2 in pregnant women at the time of delivery in our institution is quite low (4.5 %). This seroprevalence is lower than the prevalence of 10.6 % measured in the general population of the Paris area between April 6th and April 12th [17] and shouldn't be attributed to a low performance of the test. The test used is approved by the FDA and has been associated to high analytical performances with a sensitivity between 92.7 and 97.3 % and a specificity >99 % [18,19]. This low seroprevalence is possibly explained by the fact that pregnant women were more accurate in accepting and applying national recommendations to limit the spread of the virus and the risk to be infected (social distancing, use of surgical masks, use of hydro-alcoholic solutions) compared to non-pregnant individuals. Moreover, according to national recommendations, pregnant women were advised to stop professional activities after 28 WG to limit the risk of maternal infection during the third trimester. Therefore, most of the patients of our cohort didn't have any professional nor social contacts even after the end of the lockdown.

In our study, two patients with a positive SARS-Cov-2 PCR had a negative serology. The first had clinical symptoms of COVID-19 (anosmia) and an IgG ratio of 0.8 in the grey zone of the test. Therefore, this case can be considered as a false negative result of the serology. For the second patient, the PCR was a screening test performed in a private lab and the details of the results couldn't obtained. The only symptoms were a temperature at 37.8 °C. The patients delivered 6 weeks later with a negative serology (IgG index at 0.0). The sample was tested with another immunoassay (Euroimmune) and was also negative. Therefore, this case was possibly a false positive test of the PCR.

The result of our preliminary study is consistent with the recent report of SARS-CoV-2 seroprevalence among parturient women in Philadelphia [20]. Among 1293 delivering women in two centers of Philadelphia between April 4th and June 3rd 2020, 6.2 % had positive SARS-CoV-2 specific IgG and/or IgM. Another recent study performed in 3 university hospitals in Barcelona reported a higher seroprevalence of 14 % among 502 parturients. This higher seroprevalence may reflect the critical situation of COVID-19 outbreak in Spain but could also be related to the fact that the authors tested for anti-SARS-CoV-2 IgG, IgM, and IgA antibodies [21].

Many studies are ongoing in different countries to evaluate the consequences (for the mothers, the fetuses and the newborns) of COVID-19 infection during pregnancy. All these studies were designed in emergency with very little information to calculate the number of patients to include in order to achieve sufficient statistical power. The low prevalence we report in this manuscript should help study-investigators to adapt the sample size of their study while the inclusions are ongoing.

Table 2
Description of the 12 fetal losses.

	n	(%)
Gestational age at delivery		
16-17 WG	4	(33.4)
18-21 WG	3	(25.0)
22-26 WG	2	(16.7)
27-30 WG	3	(25.0)
Cause of fetal loss		
TOP	9	(75.0)
IUFD	3	(25.0)
SARS-CoV-2 IgG at delivery		
Positive	1	(8.3)
Negative	11	(91.7)

WG : weeks of gestation, IUFD : intra-uterine fetal death, TOP : termination of pregnancy.

Table 3
Characteristics of the 529 mothers and their newborns according to the anti-SARS-Cov-2 IgG testing.

	Anti-SARS-Cov-2 IgG				
	Positive (n = 25)		Negative (n = 504)		
	n/N	(%)	n/N	(%)	p-value
Maternal age					0.90
< 35 y	15/25	(60.00)	309/504	(61.31)	
≥ 35 y	10/25	(40.00)	195/504	(38.69)	
BMI					1.00
< 25	21/25	(84.00)	408/504	(80.95)	
≥ 25	4/25	(16.00)	96/504	(19.05)	
Geographic origin					0.17
Africa	7/23	(30.43)	90/496	(18.15)	
Other	16/23	(69.57)	406/496	(81.85)	
Multiple pregnancy					1.00
No	25/25	(100.00)	488/504	(96.83)	
Yes	0/25	(0.00)	16/504	(3.17)	
Gestational age at delivery					0.71
< 37 WG	1/25	(4.00)	40/504	(7.94)	
≥ 37 WG	24/25	(96.00)	464/504	(92.06)	
Mode of delivery					0.40
Vaginal	23/25	(92.00)	425/504	(84.33)	
Cesarean	2/25	(8.00)	79/504	(15.67)	
Neonatal status					0.44
Alive	24/25	(96.00)	493/504	(97.82)	
Stillbirth	1/25	(4.00)	11/504	(2.18)	

This low prevalence will certainly increase with time as SARS-CoV-2 is still actively circulating in France. The COVIPREG study is ongoing and we will be able to evaluate the evolution of the SARS-CoV-2 seroprevalence over time.

5. Conclusion

These results suggest that the seroprevalence of SARS-CoV-2 IgG in pregnant women at the time of delivery is quite low (4.7 %) approximately 2–3 months after beginning of outbreak in our region. Studies evaluating the impact of COVID-19 infection during pregnancy should take in account this information in order to adapt their sample size.

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Declaration of Competing Interest

CVF has obtained a grand from Ferring pharmaceutics for the COVIPREG study.

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