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SHORT COMMUNICATION

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The "scar" of a pandemic: Cumulative incidence of COVID-19 during the first trimester of pregnancy

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Abstract

Congenitally- or perinatally-acquired viral infections can be harmful to the fetus but data are limited about prevalence and outcomes of coronavirus disease 2019 (COVID-19) disease during the first trimester of pregnancy. We report epidemiologic data from a study investigating a cohort of women who became pregnant just before or during the COVID-19 pandemic. We recruited 138 consecutive pregnant women attending for first trimester screening (11-13 weeks of gestation) at Sant'Anna Hospital, Turin, Piedmont, Italy, during the plateau and the falling phase of the COVID-19 epidemic curve. Patients were tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulin M/immunoglobulin G antibody levels and SARS-CoV-2 detection in sera and nasopharyngeal swab samples. COVID-19 cumulative incidence during the first trimester was of 10.1% with high prevalence of asymptomatic patients (42.8%). Similar to the course of the disease in non pregnant adults, 80% to 90% of infections were not severe.The prevalence of reported symptoms was four-fold higher in SARS-CoV-2 positive patients (57%) than in those negative (13%) ($P < .001$), suggesting that direct self-testing should open doors to confirmatory testing for COVID-19. Our findings support the need for COVID-19 screening in early pregnancy in epidemic areas to plan materno-fetal health surveillance programs.

KEYWORDS

COVID-19, first trimester, pregnancy, SARS-CoV-2, seroprevalence

1 | INTRODUCTION

On 31st December 2019, the World Health Organization was informed of a cluster of pneumonia cases of unknown origin in Wuhan City, Hubei Province, China. Since then, and as of 14 June 2020, 7 789 024 cases of coronavirus disease 19 (COVID-19) have been reported with 430 173 deaths. Although there was a striking decrease in China a few weeks later, there was a rapid increase in other countries like Italy to more than 6000 per day as of the third week of March, 2020.[1]

COVID-19 is generally susceptible to all age groups, but the impact in pregnant women drawn much attention because the unique immunological state of pregnancy and the increased risk of respiratory infections. In particular, the characteristic immune

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responses during the different gestational ages, are bound to be closely related to the outcome of infection.[2]

As the disease spread, reports of the first cases of SARS-CoV-2 infection in pregnancy were documented[3-5] but evidence is based only on a few hundred patients and mainly concerns the second and third trimester of pregnancy However, viral infections can be harmful to the fetus during the first trimester of pregnancy, and whether SARS-CoV-2 is one of them may worry obstetricians.[6-8] SARS-CoV-2 is characterized by high infectivity and a substantial number of COVID-19 cases may be underdiagnosed.[9-12] Screening pregnant women has gained importance because of the high proportion of asymptomatic cases and because of the uncertainty about maternal and fetal outcomes related to COVID-19.[13,14]

Although the investigation of COVID-19 infection in the first trimester has been recommended,[15] the real prevalence of infection in early pregnancy remains to be defined.

The combined use of virus-specific antibody detection for COVID-19 and nucleic acid testing not only reduces false-negative results of molecular testing[16,17] but can also define previous and ongoing infection in a given population over a range of time.[18]

The objective of this study was to evaluate the cumulative incidence of SARS-CoV-2 infection during the first trimester of pregnancy in a highly endemic region in northern Italy.

2 | METHODS

Pregnant women attending Sant'Anna Hospital, Piedmont Region, Turin, Italy for fetal nuchal translucency measurement between 16 April and 4 June 2020 were invited to participate in the study. Blood tests for the detection of immunoglobulin G (IgG)/immunoglobulin M (IgM) non neutralizing antibodies against SARS-CoV-2 were performed and reverse transcriptase-polymerase chain reaction (RT-PCR) assays were carried out on nasopharyngeal swabs. Specific IgG neutralizing antibodies were determined in patients with at least one positive test. Blood samples were analyzed the day of collection.

A rapid automated fluorescent lateral flow CE-approved immunoassay (AFIAS COVID-19; Boditech, Gang-won-do, Korea) was used for qualitative and semi-quantitative detection of IgG/IgM non neutralizing antibodies against the spike (S) and nucleocapsid (N) viral proteins; semi-quantitative results are expressed as the cut-off index (COI) in which a COI > 1.1 indicates a positive result. Chemiluminescence CE-approved immunoassay technology was used for the semi-quantitative determination of anti-S1 and anti-S2 specific IgG neutralizing antibodies to SARS-CoV-2 (Liaison SARS-CoV-2 S1/S2 IgG; Diasorin, Saluggia, Italy): the antibody concentration is expressed as arbitrary units (AU/mL) and grades the results as positive when ≥15 AU/mL. Viral RNA extraction from the swab was performed on a MagNA Pure compact instrument (Roche, Mannheim, Germany) and analyzed using a RT-PCR assay (CFX-96; Bio-Rad, Milan, Italy) with the Liferiver Novel Coronavirus 2019-nCov real-time RT-PCR kit protocol, targeting genes N, E, and ORF1ab (Liferiver Bio-Tech, San Diego, CA).

Any seroconversion in pregnant women with their last menstruation before the date of the first reported case of COVID-19 infection in Piedmont (22 February 2020) was defined as positive, as were all RT-PCR positive cases, regardless of the last menstruation. Cumulative incidence was defined as the rate of positive cases according to the aforementioned definition.

Demographic characteristics and COVID-19-related symptoms were collected by interview.

The study was approved by the Institutional Review Board of the City of Health and Science of Turin (Reference number: 00171/2020). Written, informed consent was obtained from all participants.

The results for quantitative variables are expressed as the mean ± standard deviation and qualitative categorical variables are expressed as frequency and percentages. Quantitative variables were compared using the t test based on normal distribution. Qualitative variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Statistical analyses were performed by SAS software version 9.4 for Windows (SAS Institute, Carey, NC).

3 | RESULTS

A total of 138 women in the first trimester of pregnancy (11-13 weeks of pregnancy), attending our Institute, were included in the study and the patient adhesion rate was 88.4% (138/156). Participants were all Caucasian with an average age of 33.7 ± 4.5 years and a body-mass index of 21.7 ± 2.9 kg/m^2; 4 out of 138 (2.8%) were smokers. One hundred twenty-five patients (90.6%) conceived naturally. Eighty-five out of 138 women (61.6%) were primigravidae, 42 out of 138 (30.4%) have given birth once, 11 out of 138 (7.9%) have been pregnant more than once.

Twenty-five out of 138 pregnant women (18.1%) had comorbidities, including endocrinological and autoimmune diseases, thrombophilia, uterine abnormalities.

A total of 14 out of 138 women tested positive for anti-SARS-CoV-2 antibodies or had a positive nasopharyngeal swab for COVID-19, yielding an overall cumulative incidence of 10.1% in the first trimester; 8 out of 138 (5.8%) were only seropositive, 6 out of 138 (4.3%) were also RT-PCR positive.

In the study group 8 out of 14 (57.1%), 4 out of 14 (28.6%), and 2 out of 14 (14.3%) were positive for SARS-CoV-2 IgG, SARS-CoV-2 IgM, or both SARS-CoV-2 IgG and IgM, respectively. A total of 6 out of 14 (42.8%) RT-PCR also had a positive nasopharyngeal swab (Figure 1).

IgG neutralizing antibodies were detected in 6 out of 14 (42.8%), not correlated with symptoms (2/6 vs 4/6; $P \geq .62$), but significantly associated with a positive nasopharyngeal swab (5/6 vs 1/6; $P = .025$). The average antibody titer was 18.4 AU/mL and 1.4 COI for anti-SARS-CoV-2 IgG and IgM non neutralizing antibodies and 45.6 AU/mL for anti-SARS-CoV-2 IgG neutralizing antibodies.

No significant difference in age (32.6 ± 3.54 vs 33.9 ± 4.63; $P = .333$), body-mass index (21.3 ± 4.70 vs 21.8 ± 2.9; $P = .844$) or smoking status (0/14 vs 4/124; $P = .478$) was noted between patients testing positive and those testing negative for COVID-19.

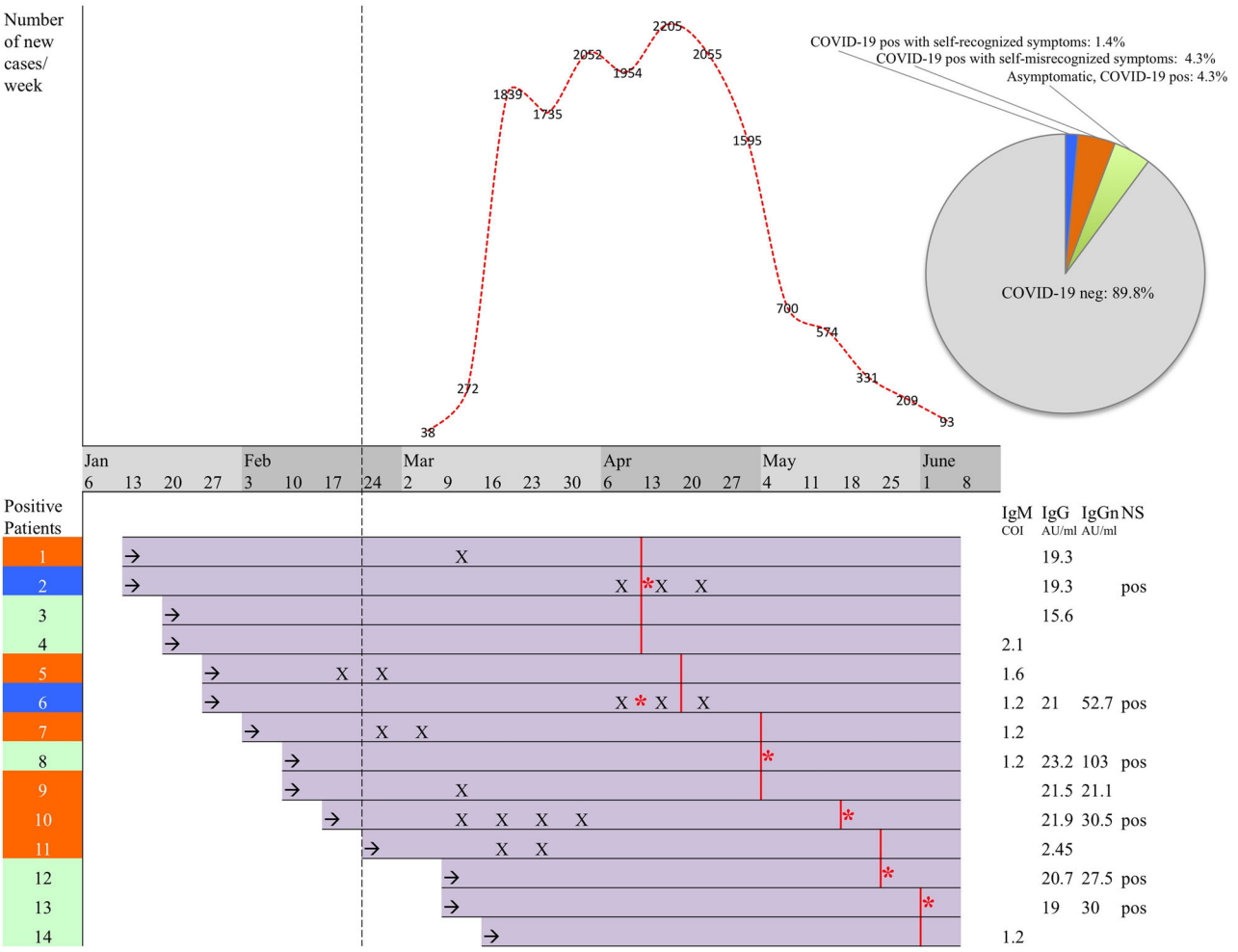

FIGURE 1 Pregnant severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive patients during coronavirus disease 2019 (COVID-19) outbreak in Turin: sero-molecular profiles and symptom status. Black arrow: last menstruation; dotted black arrow: first reported case of COVID-19 in the Piedmont Region, Italy; dotted red arrow: COVID-19 outbreak cases in Turin, weekly case increase; rectangular violet box: weeks of pregnancy; red *: molecular positive sampling; red vertical line: serological sampling; X: reported COVID-19-related symptoms. COI, cut-off index; IgGn, neutralizing immunoglobulin G; IgM, immunoglobulin M; NS, nasopharyngeal swab

Two out of 14 (14.3%) positive patients, had been diagnosed by RT-PCR for COVID-19 before 12 weeks of pregnancy because symptomatic: 6 out of 14 (42.8%) referred previous symptoms at the medical interview. Reported symptoms included low-grade fever (5/14, 35.7%), cough (4/14, 28.6%), anosmia and ageusia (3/14, 21.4%), arthralgia (2/14, 14.3%), and diarrhea (1/14, 7.1%); no pneumonia or hospital admission due to COVID-19-related symptoms was recorded. The number of symptoms suggestive of COVID-19 before enrollment in the study was higher in the women who tested positive than in those who did not (8/14 vs 16/124; $P < .001$).

4 | DISCUSSION

Previous or ongoing COVID-19 infection was detected in about one out of ten pregnant women attending the noninvasive prenatal services at our hospital, one of the largest obstetric hospitals in Europe with approximately 7000 to 8000 deliveries/year. The combined results of RT-PCR and two different serological assays, the inclusion criteria, together with the beginning of the study at the time of the pandemic outbreak allowed us to pinpoint the time of infection and seroconversion during pregnancy. Although our findings cannot be generalized, as they come from a single center located in a region with a high infection incidence, they do emphasize the need to plan a tailored obstetric management of these patients.

Between 22 March and 4 April 2020, 1.9% of symptomatic and 13.7% of asymptomatic pregnant women admitted to the New York-Presbyterian Allen Hospital and Columbia University Irving Medical Center for delivery tested positive for SARS-CoV-2 by nasopharyngeal swab.[14] Although the number of confirmed cases at the peak of the epidemic curve differs greatly between New York City and Turin (104 410 and 7939), the prevalence rate per 1000 persons was similar (1.6/1000 and 3.5/1000, respectively),[19,20] making the data comparable. The different time points of patient recruitment of the

two studies, along with the rising and the falling phase of the epidemic curve, explain the different rates of positive RT-PCR results. Given the high prevalence of infection also during the first trimester of pregnancy, we suggest that, in epidemic areas, screening for COVID-19 infection be performed in women admitted to hospital care, regardless of the trimester of pregnancy.

Moreover, our findings confirm that COVID-19 is frequently asymptomatic and should be considered in all pregnant women in areas with a high disease prevalence. Similar to the course of the disease in non pregnant adults, 80% to 90% of infections are not severe. The percentage of asymptomatic patients (42.8%) is in line with current data, suggesting that asymptomatic individuals may account for approximately 40% to 45% of SARS-CoV-2 infections.[21]

The women in the present cohort probably misrecognized that their symptoms were suggestive of COVID-19, as all but two had never been tested for SARS-CoV-2 before. The prevalence of symptoms was four-fold higher in those testing positive (57%) than in those testing negative (13%), suggesting that pregnant women in epidemic areas with symptoms should consult with their obstetrician about whether to be tested for COVID-19. Self-reported symptoms, like ageusia, anosmia, together with fever or cough, can help to identify 87.5% of symptomatic COVID-19 cases.[22]

Despite the current decline in disease incidence in some countries, pregnant women who spent the first 12 weeks of their pregnancy during the pandemic remain a population at risk because they are potential carriers of infection "scar." These patients are a special population who needs excellent care, support and long term follow up.[15]

Patient-tailored management, obstetric and fetal monitoring, and protection of the community with recommended home isolation, are the main reasons why first trimester sero-molecular screening should be promoted. Prenatal diagnostic testing provides an ideal opportunity for health care providers to plan screening.

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