



Obstetric and neonatal outcomes after SARS-CoV-2 infection in the first trimester of pregnancy: A prospective comparative study

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Abstract

Objective(s): This prospective observational cohort study aimed to evaluate whether women with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during the first trimester of pregnancy are at higher risk of adverse obstetric and neonatal outcomes compared to negative patients.

Study Design: Seromolecular testing for SARS-CoV-2 was performed at 12, 16, 21 weeks, and at delivery; the cohort was then subdivided into a first-trimester SARS-CoV-2-positive (case) group and a SARS-CoV-2-negative (control) group. The primary outcome was a composite adverse obstetric outcome, defined as the presence of either abortion, preterm delivery, preterm prelabor rupture of membranes, preeclampsia, intrauterine growth restriction, stillbirth; and a composite measure of adverse neonatal events, including either 1- and 5-min Apgar score ≤ 7 , neonatal intensive care unit admission and congenital birth defects. Maternal symptoms and antibody titer were secondarily assessed.

Results: A total of 17 of 164 women tested positive for SARS-CoV-2 (10.3%) in the first trimester. One SARS-CoV-2-positive patient who gave birth at another hospital was excluded. Composite adverse obstetric outcome was observed in 6.2% (1/16) SARS-CoV-2-positive and 10.5% (11/105) SARS-CoV-2-negative women; composite adverse neonatal outcome in 12.5% (2/16) and 7.6% (8/105), respectively. In the newborns of women who had developed IgG antibodies, the same antibodies were detected in arterial cord blood and the nasopharyngeal swab tested negative for SARS-CoV-2.

No maternal pneumonia or hospital admission due to coronavirus disease-19 were recorded.

Conclusion: Asymptomatic or mildly symptomatic women during the first trimester of pregnancy did not experience significantly more adverse events than SARS-CoV-2-negative women.

Key words: COVID-19, outcome, pregnancy, SARS-CoV-2, vertical transmission.

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Introduction

Coronavirus disease-19 (COVID-19), the infectious disease caused by the newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was officially declared a pandemic by the World Health Organization (WHO) on 11 March 2020.¹ At this writing, there is little evidence for the extent of vertical transmission of SARS-CoV-2 and its timing (in utero, intrapartum, or the early postnatal period).^{2,3} So far, the neonatal and obstetric outcomes of pregnancies infected during the first trimester have not been well documented,⁴ and there is scant information about the potential direct effects of SARS-CoV-2 infection on early embryogenesis and organogenesis.

Although no evidence has been reported for in utero transmission of other respiratory coronavirus infections, early congenital transmission of SARS-CoV-2 in humans is plausible by analogy with animal models of coronavirus disease.⁵ Also, increased thrombotic risk and inflammatory activation make the placenta a potential target of pathophysiological processes that could indirectly affect pregnancy outcomes in patients with COVID-19.^{6–8}

The primary aim of this study was to determine whether women testing positive for SARS-CoV-2 during the first trimester of pregnancy are at higher risk of composite adverse obstetric and neonatal outcomes compared to a cohort of healthy pregnant women. The secondary aim was the occurrence of all the individual outcomes considered for the composite primary aim. Finally, maternal symptoms were evaluated.

Materials and Methods

Study population

Consecutive 12-week pregnant patients attending our institution for noninvasive prenatal diagnosis or admitted to the care units for COVID-19-related symptoms between 16 April and 22 June 2020 were invited to participate in the study. Nasopharyngeal (NP) swab samples were taken for reverse transcriptase-polymerase chain reaction (RT-PCR) assay to detect SARS-CoV-2; blood samples taken for prenatal screening were obtained to detect antibodies against SARS-CoV-2. Semi-quantitative detection of IgG/IgM non-neutralizing antibodies (nNAbs) was performed using an automated (AFIAS™ COVID-19, Boditech Med Inc., Gang-won-do, Korea) lateral flow immunochromatographic assay; semi-quantitative detection of IgG neutralizing antibodies

(NAbs) was performed by chemiluminescent immunoassay (Liaison® SARS-CoV-2 S1/S2 IgG, DiaSorin, Saluggia, Italy). Both serologic assays had emergency use authorization.

Only women with the last menstruation no later than 1 month after the date of the first case of COVID-19 infection reported in Piedmont (22 February 2020) were considered eligible for inclusion in the study, so as to exclude the possibility of COVID-19 seroconversion before pregnancy (Figure 1). Indeed, the duration of SARS-CoV-2 virus shedding varies from 6 to 8 weeks in upper respiratory tract samples and 5 weeks in feces.^{9,10} This strict recruitment criterion allowed us to define seropositivity as seroconversion that had occurred during pregnancy. Exclusion criteria were: delivery scheduled at another hospital, inability to give informed consent, and age less than 18 years.

Study design

The protocol for this prospective, observational cohort study was approved by the Institutional Review Board of the City of Health and Science of Turin (reference number: 00171/2020).

Positive patients were defined as women who tested positive for NAbs or nNAbs or NP swab. The virological test results at 12 weeks of pregnancy were collected and the cohort was divided into two groups: first-trimester SARS-CoV-2-positive patients, both asymptomatic and symptomatic (case group), and SARS-CoV-2-negative patients (control group). The entire cohort was seromolecular tested a second time at 16 weeks, a third time at 21 weeks, and then at delivery. The control group patients who tested positive at the second, third, or fourth test were excluded from the study so as to select only first-trimester seroconversions avoiding biases. Both groups were followed longitudinally throughout pregnancy by the study team. Demographics, obstetric, neonatal outcomes, and COVID-19-related maternal symptoms were collected. COVID-19 was categorized into mild, moderate, or severe. Mild COVID-19 defines as the presence of mild symptoms (e.g., fever, cough, or change in taste or smell) without dyspnea, while the moderate or severe infection is defined as the presence of lower respiratory tract disease. In moderate cases, SpO₂ is $\geq 94\%$ while one of the following is required to define the severe cases: respiratory rate > 30 breaths/min or SpO₂ $< 94\%$ or lung infiltrates $> 50\%$.¹¹ The primary outcome of this study was to compare the incidence of a composite measure of adverse obstetric events, including at least one of

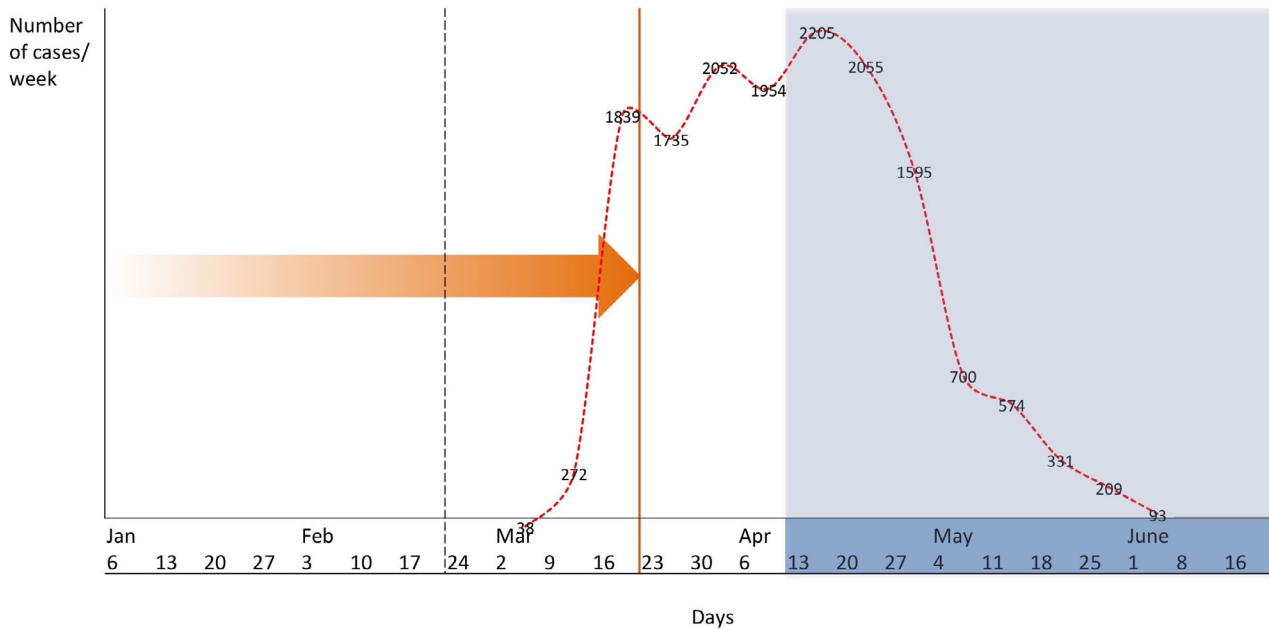


FIGURE 1 Last menstruation criterion for inclusion and recruitment. Blue area: recruitment period; dotted black line: first case of COVID-19 reported in Piedmont, Italy; dotted red line: COVID-19 outbreak cases in Turin, weekly case increase; vertical orange line: date of the last menstruation upper limit of inclusion

the following: abortion, preterm delivery, and preterm prelabor rupture of membranes (PPROM) (before 37 weeks), preeclampsia, intrauterine growth restriction (IUGR), stillbirth; and a composite measure of adverse neonatal events, including at least one of the following: 1- and 5-min Apgar score ≤ 7 , neonatal intensive care unit (NICU) admission and congenital birth defects.

At delivery of patients with a previously confirmed diagnosis of SARS-CoV-2 positivity, further testing for SARS-CoV-2 were collected: placental, vaginal, rectal, and colostrum maternal swabs, as well as the neonatal NP. Arterial umbilical cord blood samples were tested for nNabs and Nabs immediately after delivery. The placenta was sent for microscopic examination and histopathological characterization.

Statistical analysis

Pearson's chi-square test or Fisher's exact test as appropriate was used for categorical variables; otherwise, Student's *t*-test for normally distributed variables or Wilcoxon matched-pairs signed-ranks test was performed. For all comparisons, differences were considered statistically significant if $p < 0.05$. Statistical analysis was performed using SAS software version 9.4 for Windows (SAS Institute, Carey, NC, USA).

Sample size calculation was not possible because the effect size of COVID-19 on the outcomes evaluated in this study was unknown and could not be estimated on the basis of previous publications. Furthermore, disease prevalence was unpredictable as it is dependent on the epidemic curve at enrollment. Finally, the cohort size was restricted according to the criteria, as further recruitment beyond 22 June would have precluded the eligibility criterion for the last menstruation.

Results

A total of 164 women at the first trimester of pregnancy, attending our Institute during the recruitment period, were included in the study. The attendance rate was 85.4% (164/192): 17/164 women tested seropositive for anti-SARS-CoV-2 IgG and/or IgM antibodies or had a positive NP swab for SARS-CoV-2 at 12 weeks pregnancy, yielding an overall COVID-19 cumulative incidence of 10.4% in the first trimester. In detail, 16 of 164 (9.7%) tested positive for nNabs; a positive NP swab without antibody response was recorded in one of 17. Nine of the 16 (56.2%) who tested positive for nNabs (IgM and/or IgG) were also

positive for NAbs (IgG). The NP swab tested positive in nine of 16 (56.2%).

The data from the case group ($n = 16$) and the control group ($n = 105$) were entered into the final analysis; women who had seroconverted during the second ($n = 3$) or third ($n = 14$) trimester or were lost to follow-up ($n = 25$) were excluded from the analysis, as was one SARS-CoV-2-positive patient who gave birth at another hospital (Figure 2).

There were no differences between groups for anthropometric variables and obstetric history; maternal comorbidities were similar between the two groups (Table 1).

Obstetric outcomes

There were no differences between the two groups for incidence of gestational age at delivery and the incidence of composite adverse obstetric outcome (Table 2); in women with and without SARS-CoV-2 infection, the primary aim (obstetric complications) occurred in 6.2% (1/16) and 10.5% (11/105), respectively.

Histopathological features of the placenta from the 16 SARS-CoV-2-positive women are presented in Table S1. The most common findings were villous hypoplasia ($n = 6$), decidual hemorrhage ($n = 5$), low-grade

chronic villitis ($n = 4$), chronic lymphoplasmacellular deciduitis ($n = 4$), fetal vascular malperfusion (FVM) ($n = 4$), and subacute deciduitis ($n = 4$).

Neonatal outcomes

There were no differences in birth weight, Apgar score or umbilical artery pH. The primary aim (neonatal complications) occurred in 12.5% (2/16) SARS-CoV-2 positive-women and 7.6% (8/105) SARS-CoV-2 negative-women (11/105) ($p = 0.86$) (Table 3). No newborn tested positive for SARS-CoV-2 at delivery. The same antibodies in the arterial cord blood were detected in the newborns of the women who had developed IgG antibodies for SARS-CoV-2. The mean neonatal titer of NAbs and of nNAbs at delivery was 53.43 ± 43.15 AU/mL and 6.09 ± 7.04 COI, respectively.

A suspected fetal malformation was detected at the second-trimester fetal anatomic survey in the case group. The 20-week screen scan of a 35-year-old COVID-19-positive patient showed slight fetal right ventricular dominance, left-sided superior vena cava draining into the right atrium via the coronary sinus, and severe atrial septal defect. Invasive prenatal testing (amniocentesis) was performed: the amniotic fluid sample tested negative for SARS-CoV-2 and

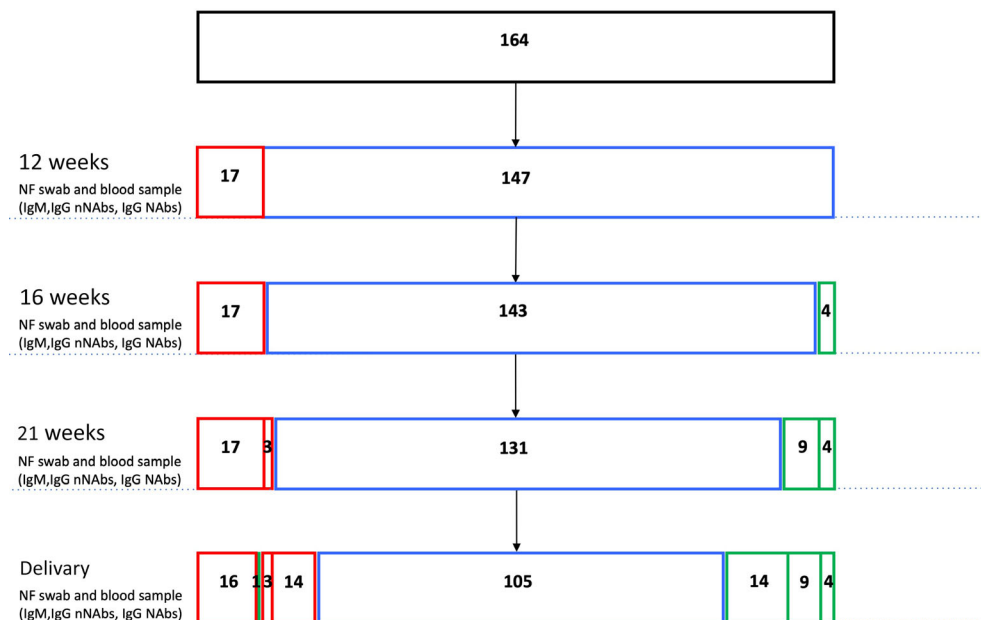


FIGURE 2 Study flow diagram: Case ascertainment and control selection. Blue box, COVID-19 negative patients; green box, patients excluded; nNAbs, non-neutralizing antibodies; NAbs, neutralizing antibodies; NP, nasopharyngeal; red box, COVID-19 positive patients; orange arrow, patients excluded; WKS, weeks gestation

TABLE 1 Baseline characteristics, clinical findings in COVID-19-positive and -negative patients

Clinical findings	COVID-19 positive <i>n</i> = 16		COVID-19 negative <i>n</i> = 105	<i>p</i> -value
	<i>n</i> (%) or mean \pm SD		<i>n</i> (%) or mean \pm SD	
Age (years)	31.9 \pm 4.0		34.3 \pm 4.1	0.03
BMI prior to pregnancy (kg/m ²)	22.7 \pm 3.1		22.7 \pm 4.3	0.94
Gravidity				0.82
	0	9 (56.2)	65 (61.9)	
	1	6 (37.5)	29 (27.6)	
	2	1 (6.3)	9 (8.6)	
	3	0 (0)	2 (1.9)	
Previous Abortions	0	14 (87.5)	75 (71.4)	0.18
	1	0 (0)	22 (21)	
	2	1 (6.2)	6 (5.7)	
	3	1 (6.3)	2 (1.9)	
ART therapy	2 (12.5)		9 (8.6)	0.97
Smoking history	2 (12.5)		17 (16.2)	0.99
Thyroid disease	1 (6.3)		14 (13.3)	0.69
Autoimmune diseases	0 (0)		4 (3.8)	0.97
Thrombophilia	1 (6.3)		6 (5.7)	0.62
Uncontrolled DM	0 (0)		0 (0)	—
Thrombophilia	1 (6.3)		6 (5.7)	0.62
Uterine anomalies	0 (0)		6 (5.7)	0.72
Chronic kidney disease	0 (0)		2 (1.9)	0.62
Chronic pulmonary disease	0 (0)		1 (0.9)	0.28
Immunocompromised state	0 (0)		3 (2.9)	0.86
Cardiopathy	0 (0)		1 (0.9)	0.28
Asthma	0 (0)		0 (0)	—
Hypertension	0 (0)		1 (0.9)	0.28
Liver disease	0 (0)		0 (0)	—
Neurologic conditions	0 (0)		2 (1.9)	0.62
Thalassemia	0 (0)		2 (1.9)	0.62

Abbreviations: ART, assisted reproductive technique; BMI, body-mass index; DM, diabetes mellitus.

TABLE 2 Obstetric outcomes in COVID-19 positive and negative patients

Clinical findings	COVID-19 positive	COVID-19 negative	<i>p</i> -value
	<i>n</i> = 16 <i>n</i> (%) or mean \pm SD	<i>n</i> = 105 <i>n</i> (%) or mean \pm SD	
Gestational age at delivery	271.7 \pm 10.6	272.7 \pm 15.5	0.82
Composite adverse obstetric outcome	1 (6.2)	11 (10.5)	0.93
Spontaneous abortion	0 (0)	2 (1.9)	0.62
PPROM	1 (6.3)	3 (2.9)	0.97
Preterm birth	1 (6.3)	9 (8.6)	0.86
Preeclampsia	0 (0)	3 (2.9)	0.85
IUGR	0 (0)	3 (2.9)	0.85
Stillbirth	0 (0)	0 (0)	—
Caesarean delivery	5 (31.2)	26 (24.8)	0.81
Vacuum assisted delivery	1 (6.3)	5 (4.8)	0.72
Vaginal delivery	10 (62.5)	72 (68.6)	0.84

Abbreviations: IUGR, intrauterine growth restriction; PPRM, preterm prelabor rupture of membranes.

aneuploidies were excluded. Ultrasound prenatal findings without hemodynamic impairment and complex cardiac anomalies were revealed at postnatal

assessment in the NICU, along with a melanocytic nevus on the scalp, a series of five smaller nevi on the back, and a pigmented lesion in the iris. At inclusion

TABLE 3 Neonatal data

	Newborns from COVID-19-positive patients	Newborns from COVID-19-negative patients	<i>p</i> -value
	<i>n</i> = 16 <i>n</i> (%) or mean \pm SD	<i>n</i> = 105 <i>n</i> (%) or mean \pm SD	
Birth weight (g)	3270 \pm 429	3239.1 \pm 565.2	0.83
Umbilical artery pH	7.29 \pm 0.07 ^a	7.29 \pm 0.01 ^b	0.79
Positive nasopharyngeal swab	0 (0)	0 (0)	—
Composite adverse neonatal outcome	2 (12.5)	8 (7.6)	0.86
1- and 5-min Apgar score \leq 7	1 (6.3)	3 (2.8)	0.43
NICU admission	1 (6.3)	6 (5.7)	0.63
Congenital birth defect	1 (6.3)	7 (6.7)	0.63

^aMissed: 2 (12.5). and ^bMissed: 30 (28.6).

in the study (12 weeks), she was asymptomatic and her blood profile showed COVID-19 IgG nNabs (19.28 COI) without evidence of Nabs. Integrated screening testing yielded negative results.

Maternal outcomes

No pneumonia or hospital admission due to COVID-19-related symptoms were recorded. In the case group, five of 17 (29.4%) patients who tested positive at RT-PCR for SARS-CoV-2 before 12 weeks of pregnancy self-reported as being symptomatic, including three who attended prenatal screening tests under the protocol for SARS-CoV-2-positive patients; three of 17 (17.6%) were asymptomatic; nine of 17 (52.9%) had self-misrecognized symptoms and reported symptoms only at history taking. Reported symptoms included fever (7/14, 50%), anosmia and ageusia (6/14, 42.8%), cough (5/14, 35.7%), arthralgia (4/14, 28.6%), diarrhea (3/14, 21.4%), and dyspnea (2/14, 14.3%).

The mean antibody titer at admission was 19.82 \pm 2.79 COI and 1.18 \pm 0.40 COI for anti-SARS-CoV-2 IgG and IgM nNabs, respectively, and 43.72 \pm 29.13 AU/mL for anti-SARS-CoV-2 IgG Nabs. The mean maternal titer of nNabs and Nabs at delivery was 6.09 \pm 7.04 COI and 53.43 \pm 43.15 AU/mL, respectively. Placental, vaginal, and rectal swabs collected at delivery all tested negative. All colostrum maternal swabs tested negative.

Discussion

Main findings

There was no significantly different rates of composite unfavorable obstetric and neonatal outcomes between

COVID-19-positive women in the first trimester compared to a cohort of SARS-CoV-2-negative women matched for gestational age. There was no evidence of vertical transmission; a single case of thoracic venous anomaly associated with a cardiac anomaly (atrial septal defect) was recorded. After excluding congenital chromosomal anomalies; however, no association with COVID-19 could be clearly demonstrated. Finally, the incidence of maternal symptoms was negligible.

Strengths and limitations

The main strengths and limitations of our prospective study stem from the strict inclusion criterion that precluded recruitment of patients beyond 1 month of the date of the first reported COVID-19 case in Piedmont. This ensured the selection of cases with an infection that most certainly occurred during the first trimester of pregnancy; however, it also restricted the sample size and increased the probability of a type II error.

The SARS-CoV-2-negative (control) group was recruited at the same center and in the same timeframe as the SARS-CoV-2-positive (case) group; thus, establishing similar conditions and minimizing selection biases. Unlike previous reports,^{10,11} the entire cohort underwent repeated seromolecular testing until delivery. Control group patients who tested positive at subsequent tests were excluded from the study. In this way, a noninfected control group was maintained. In addition, since all the women underwent sero and molecular testing, also those asymptomatic patients testing negative for antibodies but positive for RT-PCR were included in the case group.

Finally, the case group was a relatively healthy, real-world cohort without underlying uncontrolled medical conditions associated with increased severity of coronavirus infection. Moreover, although hospitalized

patients were also included, a selection bias cannot be fully ruled out since the recruitment criteria may have allowed the inclusion of asymptomatic women, as SARS-CoV-2-positive patients with serious symptoms would not have attended the scheduled outpatient hospital visits.

Interpretation

There is a paucity of data on the risks associated with SARS-CoV-2 infection during the first trimester of pregnancy. The bulk of the literature consists of reports on women in the second and the third trimester of pregnancy and many studies lack a control group. There are only two prospective studies that include patients who acquired the infection in the first trimester.^{12,13} However, at present writing, follow-up data have been obtained until mid-gestation and information on delivery is likely to be forthcoming in future reports.

Consistent with our previous work,¹⁴ in the present study, we did not find evidence of increased rate of fetal defects or abnormal fetal growth at delivery. Our previous and present findings may be reassuring for women exposed to SARS-CoV-2 infection during early pregnancy, as it does not appear to be associated with either an increased risk of early pregnancy loss¹⁵ or subsequent complications such as preterm birth, preeclampsia or IUGR. Moreover, the neutralizing-antibody titer seems to persist at least until delivery¹⁶ and such pregnancies could benefit from the transplacental passage of antibodies, which are critical to protect infants during the first months of life.

Most descriptive studies that support an association between SARS-CoV-2 infection and adverse birth outcomes involved symptomatic or severely ill women in the second/third trimester. SARS-CoV-2 infection seems to be associated with higher rates of symptomatic disease and severity in third- compared to first-trimester pregnancy,^{12,17,18} probably because the third trimester is associated with major hemodynamic and respiratory changes that might predispose a pregnant woman to a more severe clinical course of COVID-19.¹⁹ Moreover, symptomatic COVID-19-positive women were noted to have a modest, albeit significant, increase in the risk of infection-related obstetric morbidity and adverse outcomes, regardless of the trimester of infection.¹² Our study cohort was composed of relatively young healthy women without apparent risk factors for severe COVID-19. Whether the

favorable outcomes were due to these low risk characteristics remains arguable.

We recorded no unfavorable perinatal outcomes in our cohort and no cases of infection by vertical transmission in utero, intrapartum or postpartum. While in utero SARS-CoV-2 transmission is possible, viremia due to SARS-CoV-2, although infrequent (10%), appears to be more likely to occur in women with severe disease.¹⁸ Also, viral infection of the cells at the maternal-fetal interface is a necessary but not sufficient condition to induce direct fetal teratogenic effects. Organs without ACE2 expression are not the target of virus-related insult. There is conflicting evidence for the expression of ACE2 and TMPRSS2 receptors at the fetal organs.^{20–23} The cardiac malformation recorded in a newborn in a COVID-19-positive mother was not unequivocally traceable to the effect of SARS-CoV-2 infection. Although maternal viral infection in early pregnancy may be associated with an increased risk of CHDs in the offspring, it is still uncertain whether SARS-CoV-2 can cause cardiac malformations.²⁴ In our patient, the RT-PCR for SARS-CoV-2 in the amniotic fluid sample was negative, providing no support for a specific etiological role of SARS-CoV-2 infection.

Rectal swabs collected at delivery tested negative and SARS-CoV-2 fecal contamination of the neonatal oro/nasopharynx during vaginal birth was excluded, as would be expected in women who were infected early during pregnancy.^{25–27}

Finally, SARS-CoV-2 can be associated with vascular damage, including hypercoagulopathy in pregnant women and ischemic injury to the placenta. SARS-CoV-2 could indirectly affect the fetus via this route without direct infection of placental tissues. Most of the available data on histopathological placental findings derive from patients who contracted SARS-CoV-2 during the third trimester of pregnancy. A systematic literature review reported findings consistent with fetal and/or maternal vascular malperfusion in 35.3% and 46% of placentas, respectively.²⁸ In our cohort, we also identified findings suggestive of FVM in several patients (4/16, 25%), including one high-grade FVM, with no repercussions on the newborn.

Inflammatory changes are another commonly reported finding in the placenta from COVID-19-positive patients. In a recent case-control study, a higher prevalence of chronic villitis of unknown etiology (VUE) was observed after limiting the comparison between the placentas delivered by asymptomatic COVID-19 patients

and those from the controls.²⁹ We observed VUE in the present series (4/16 patients, 25%). Chronic villitis/VUE can be caused by autoimmune phenomena or viral infections,^{30,31} so it is not surprising that a subset of placentas delivered after SARS-CoV-2 infection may show changes consistent with VUE. Although VUE in general has been suggested to be associated with adverse obstetrical outcomes such as IUGR, preeclampsia, stillbirth, and preterm labor,³² the obstetric outcomes in the present study did not differ between the COVID-19-positive cases and the COVID-19-negative controls probably because the VUE were low-grade. This observation is consistent with previous data that reported placental changes in COVID-positive pregnancies without an apparent impact on neonatal outcomes.^{28,33} Our data suggest that SARS-CoV-2 infection during the first trimester of pregnancy may cause some subclinical placental alterations but the clinical impact seems negligible.

Conclusions

We found no evidence for unfavorable obstetric and neonatal outcomes in this cohort of patients testing positive for SARS-CoV-2 infection. Although our data cannot be generalized, as they come from patients with asymptomatic or mild infection, they do emphasize the need for large, multicenter observational studies or meta-analyses to rule out potential etiopathogenetic links between SARS-CoV-2 infection in early pregnancy and adverse obstetrics and neonatal events. Such findings are pivotal to guide correct pre-conception counseling on the risks of COVID-19 infection during pregnancy and to plan follow-up during pregnancy and reduce fetomaternal and neonatal morbidity.

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Conflict of Interest

None declared.

Author Contributions

Stefano Cosma and Andrea Carosso: Conceptualization; Data interpretation; Writing - original draft; Writing - review and editing. **Jessica Cusato and Valeria Ghisetti:** Investigation; Resources. **Giulio Mengozzi and Raffaella Mazzone:** Formal analysis. **Fulvio Borella, Federica Bevilacqua, Luca Bertero and Marialuisa Bovetti:** Data curation. **Giovanni Di Perri and Chiara Benedetto:** Project administration; Supervision; Funding acquisition; Writing - review and editing. All authors reviewed and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Coronavirus Disease (COVID-19)—events as they happen. Available at: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen>. Accessed 28 Mar 2020, 2020.
2. Definition and categorization of the timing of mother-to-child transmission of SARS-CoV-2. Available from: <https://www.who.int/publications/i/item/WHO-2019-nCoV-mother-to-child-transmission-2021.1>. Accessed 14 Mar 2021, 2021.
3. Kotlyar AM, Grechukhina O, Chen A, Popkhadze S, Grimshaw A, Tal O, et al. Vertical transmission of coronavirus disease 2019: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2021;224(1):35–53.e3.
4. 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.
5. Singh A, Singh RS, Sarma P, Batra G, Joshi R, Kaur H, et al. A comprehensive review of animal models for coronaviruses: SARS-CoV-2, SARS-CoV, and MERS-CoV. *Viral Sin*. 2020;35(3):290–304.
6. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(4):844–7.
7. Schett G, Sticherling M, Neurath MF. COVID-19: risk for cytokine targeting in chronic inflammatory diseases? *Nat Rev Immunol*. 2020 May;20(5):271–2.
8. Bertero L, Borella F, Botta G, Carosso A, Cosma S, Bovetti M, et al. Placenta histopathology in SARS-CoV-2 infection: analysis of a consecutive series and comparison with control cohorts. *Virchows Arch*. 2021;1:1–14.

9. Sun J, Tang X, Bai R, Liang C, Zeng L, Lin H, et al. The kinetics of viral load and antibodies to SARS-CoV-2. *Clin Microbiol Infect.* 2020;**26**(12):1690.e1–4.
10. Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. *Lancet Microbe.* 2021;**2**(1): e13–22.
11. Gandhi RT, Lynch JB, Del Rio C. Mild or moderate Covid-19. *N Engl J Med.* 2020;**383**(18):1757–66.
12. Crovetto F, Crispi F, Llorba E, Pascal R, Larroya M, Trilla C, et al. Impact of SARS-CoV-2 infection on pregnancy outcomes: a population-based study. *Clin Infect Dis.* 2021;**73**(10): 1768–75. <https://dx.doi.org/10.1093/cid/ciab104>
13. la Cour FN, Egerup P, Hviid KVR, et al. SARS-CoV-2 in first trimester pregnancy: a cohort study. *Hum Reprod.* 2021;**36**(1): 40–7.
14. Cosma S, Carosso AR, Borella F, Cusato J, Bovetti M, Bevilacqua F, et al. Prenatal biochemical and ultrasound markers in COVID-19 pregnant patients: a prospective case-control study. *Diagnostics (Basel).* 2021;**11**(3):398.
15. Cosma S, Carosso AR, Cusato J, et al. Coronavirus disease 2019 and first-trimester spontaneous abortion: a case-control study of 225 pregnant patients. *Am J Obstet Gynecol.* 2020; **S0002-9378**(20):31177–7.
16. Cosma S, Carosso AR, Corcione S, Cusato J, Borella F, Antonucci M, et al. Longitudinal analysis of antibody response following SARS-CoV-2 infection in pregnancy: from the first trimester to delivery. *J Reprod Immunol.* 2021; **144**:103285.
17. Cosma S, Borella F, Carosso A, Sciarrone A, Cusato J, Corcione S, et al. The "scar" of a pandemic: cumulative incidence of COVID-19 during the first trimester of pregnancy. *J Med Virol.* 2021;**93**(1):537–40.
18. Di Mascio D. WAPM (the World Association of Perinatal Medicine) working group on COVID-19. Maternal and perinatal outcomes of pregnant women with SARS-COV-2 infection. *Ultrasound Obstet Gynecol.* 2021;**57**(2):232–41.
19. D'Antonio F, Sen C, Mascio DD, et al. Maternal and perinatal outcomes in high vs low risk-pregnancies affected by SARS-COV-2 infection (Phase-2): the WAPM (World Association of Perinatal Medicine) working group on COVID-19. *Am J Obstet Gynecol MFM.* 2021;**100329**:71–8.
20. Andersson MI, Arancibia-Carcamo CV, Auckland K, et al. SARS-CoV-2 RNA detected in blood products from patients with COVID-19 is not associated with infectious virus. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7689603/>. Accessed 14 Mar 2021.
21. Rajagopalan S, Long EO. Cell atlas reveals the landscape of early pregnancy. *Nature.* 2018;**563**(7731):337–8.
22. Hecht JL, Quade B, Deshpande V, Mino-Kenudson M, Ting DT, Desai N, et al. SARS-CoV-2 can infect the placenta and is not associated with specific placental histopathology: a series of 19 placentas from COVID-19-positive mothers. *Mod Pathol.* 2020;**33**(11):2092–103.
23. Faure-Bardon V, Isnard P, Roux N, Leruez-Ville M, Molina T, Bessieres B, et al. Anatomical and timely assessment of protein expression of angiotensin -converting enzyme 2, SARS-CoV-2 specific receptor, in fetal and placental tissues: new insight for perinatal counseling. *Ultrasound Obstet Gynecol.* 2020;**57**(2):242–7.
24. Ye Z, Wang L, Yang T, Chen L, Wang T, Chen L, et al. Maternal viral infection and risk of fetal congenital heart diseases: a meta-analysis of observational studies. *J Am Heart Assoc.* 2019;**8**(9):e011264.
25. Carosso A, Cosma S, Serafini P, Benedetto C, Mahmood T. How to reduce the potential risk of vertical transmission of SARS-CoV-2 during vaginal delivery? *Eur J Obstet Gynecol Reproduc Biol.* 2020;**250**:246–9.
26. Carosso A, Cosma S, Borella F, Marozio L, Coscia A, Ghisetti V, et al. Pre-labor anorectal swab for SARS-CoV-2 in COVID-19 pregnant patients: is it time to think about it? *Eur J Obstet Gynecol Reproduc Biology.* 2020;**249**:98–9.
27. Carosso A, Cosma S, Benedetto C. Vaginal delivery in COVID-19 pregnant women: anorectum as a potential alternative route of SARS-CoV-2 transmission. *Am J Obstet Gynecol.* 2020;**223**(4):612.
28. Sharps MC, Hayes DJL, Lee S, Zou Z, Brady CA, Almoghrabi Y, et al. A structured review of placental morphology and histopathological lesions associated with SARS-CoV-2 infection. *Placenta.* 2020;**101**:13–29.
29. Patberg ET, Adams T, Rekawek P, Vahanian SA, Akerman M, Hernandez A, et al. Coronavirus disease 2019 infection and placental histopathology in women delivering at term. *Am J Obstet Gynecol.* 2020;**S0002-9378** (20):31194–7.
30. Becroft DM, Thompson JM, Mitchell EA. Placental villitis of unknown origin: epidemiologic associations. *Am J Obstet Gynecol.* 2005;**192**(1):264–71.
31. Meijer WJ, Wensing AMJ, Bruinse HW, Nikkels PGJ. High rate of chronic villitis in placentas of pregnancies complicated by influenza a/H1N1 infection. *Infect Dis Obstet Gynecol* 2014;**2014**:768380, 1, 5.
32. Kim CJ, Romero R, Chaemsaithong P, Kim J-S. Chronic inflammation of the placenta: definition, classification, pathogenesis, and clinical significance. *Am J Obstet Gynecol.* 2015; **213**(4 Suppl):S53–69.
33. Wong YP, Khong TY, Tan GC. The effects of COVID-19 on placenta and pregnancy: what do we know so far? *Diagnostics (Basel).* 2021;**11**(1):94.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Placental histopathological findings in women with SARS-CoV-2 infection during the first trimester of pregnancy