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Mild COVID-19 among pregnant women managed with home self-isolation in Lebanon: A prospective cohort study

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Abstract

Objective: Although mild coronavirus disease 2019 comprises the vast majority of cases during and after pregnancy, it has not been adequately explored, and the medical course and pregnancy outcomes remain enigmatic. This study aimed to describe the course of mild coronavirus disease 2019 infection during pregnancy among non-hospitalized women and assess the short- and mid-term maternal and neonatal outcomes.

Methods: This was a prospective cohort study of successive cases of confirmed COVID-19 infection during pregnancy with no or mild symptoms. Patients with severe or critical disease were excluded. The included patients were followed regularly throughout pregnancy and at least three months after delivery. Outcomes included composite adverse maternal outcomes (early pregnancy loss, preterm birth, gestational diabetes mellitus, or gestational hypertension/preeclampsia) and composite adverse neonatal outcomes (neonatal intensive care unit admission, small for gestational age, congenital anomalies, or neonatal death). The incidence of long COVID-19 was also calculated.

Results: Seventy-two cases were available for analysis (n=20, n=31, and n=21 were infected during the first, second, and third trimesters, respectively). Of them, 29 (40.2%) were asymptomatic at diagnosis. The most common symptoms were fatigue, fever, and myalgia. Adverse pregnancy outcomes were rare. No difference was observed between symptomatic and asymptomatic patients. Moreover, infection timing did not impact outcomes. The overall frequency of long coronavirus disease 2019 was approximately 47.2%.

Conclusion: Mild Covid-19 infection during pregnancy is associated with a favorable prognosis. Similar to non-pregnant infected individuals, it may progress to more severe forms and Long-Covid-19 may persist.

Keywords: COVID-19, disease severity, expectant management, pregnancy, telemedicine

Introduction

Pregnancy, characterized by modulation of the immune response, places women at increased vulnerability to respiratory infections such as influenza.[1] Coronavirus disease 2019 (COVID-19) is a respiratory illness that may lead to severe pneumonia and acute respiratory distress syndrome (ARDS). In severe cases, it may evolve to multiple organ failure as well. In the early stages of the recent global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), little information was available on its impact on pregnancy. However, accumulated data obtained previously from epidemics incurred by two closely related coronaviruses (Middle East respiratory syndrome coronavirus in 2002–2003 and SARS-CoV in 2012) indicated that infection during pregnancy can result in preterm birth, miscarriage, stillbirth, and fetal growth restriction associated with placental insufficiency but not vertical transmission.[2,3]

Moreover, like most respiratory infections caused by influenza-like viruses, there is a wide array of clinical forms ranging from mild asymptomatic to severe illness; however, the majority of cases during and outside pregnancy are clinically mild disease. The emergence of early reports on COVID-19 revealed high infectivity and an association with increased morbidity and mortality rates,[4] particularly among individuals who are obese, are of advanced maternal age, are immunosuppressed, or have comorbidities.[5,6] Consequently, most studies have

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focused on severe COVID-19 in patients hospitalized during late pregnancy,[6-8] whereas little is known about the more prevalent mild form during pregnancy whose medical course and outcomes remain unclear.

This study aimed to assess and report the short- and mid-term outcomes of pregnant women with mild COVID-19 in Lebanon.

Methods

Study design and population

This prospective observational cohort study was conducted at the outpatient and private clinics of a single institution, between June 1, 2021, and February 28, 2022. We included all consecutive pregnant women with SARS-CoV-2 confirmed on reverse transcription polymerase chain reaction (RT-PCR) from a nasopharyngeal swab who were either asymptomatic or developed only mild symptoms according to the World Health Organization (WHO) classification.[9] RT-PCR was performed either for symptoms of infection or for exposure to positive cases. We excluded patients who were hospitalized or developed severe or critical disease.

Women included in this cohort reported the infection to their obstetricians and were instructed to practice self-isolation for 2 weeks. They resumed regular antenatal visits once the RT-PCR results were negative and were followed regularly throughout pregnancy and the postpartum period. The follow-up of medical status was continued for at least 3 months after delivery through a telephone interview by the assigned researchers.

This study was approved by the local institutional review board (no. 10052021), and informed consent was obtained from the participating women according to local regulations.

Abbreviated follow-up protocol of patients with positive SARS-CoV-2 RT-PCR results

The study period coincided with the spread of the alpha (B.1.1.7), delta (B.1.617.2), and omicron (B.1.1.529) subtypes of SARS-CoV-2. During this period, pregnant patients with confirmed mild or asymptomatic COVID-19 were instructed to practice home self-isolation with appropriate protective measures if their clinical status was reassuring. They were followed by their obstetricians via phone calls to assess illness severity and the manifestation of any worrying symptoms.[10] As this was an observational study, no standardized triaging questionnaire was imposed on the obstetricians; however, the presence of dyspnea, tachypnea, a persistent high-grade fever, cough, or hemoptysis was the most common reason for urging patients to assess their oxygen saturation using pulse oximetry or seek medical advice directly at the emergency department. Moreover, the patients were instructed to report the persistence or deterioration of symptoms and the appearance of new symptoms during their voluntary home quarantine by maintaining continuous daily phone calls to update the obstetricians about their clinical condition. Patients with suspected disease progression were referred to a designated large central public hospital with appropriate resources for care and management.

Data collection and variables definition

Information related to demographic data and past medical, obstetrical, and surgical histories were collected from the patients' antenatal records at the clinics. Data about the infection, such as gestational age (GA) when the RT-PCR was first positive and first negative, the reason for the RT-PCR, symptoms at initial presentation, self-isolation duration, medications received, and number of COVID-19 infections contracted during the current pregnancy along with COVID-19 vaccination history, were obtained by patient self-reporting. Infection duration was calculated in days as the time between positive and negative RT-PCR results.

Pregnancy data were collected from our maternity unit and included GA at delivery, mode of delivery, and maternal morbidities (preterm delivery, preeclampsia [PET], and gestational hypertension [GHTN]/gestational diabetes mellitus [GDM]), birth weight, and Apgar scores. Prematurity was defined as delivery before 37 weeks of gestation (WG).

Abnormal symptoms emerging or persisting after convalescence (long COVID) according to the WHO definition[11] were gathered from antenatal records and by patient self-reporting until at least 3 months after delivery via telephone interview. Long COVID occurs in individuals within 3 months post-infection. According to the WHO, common symptoms include fatigue, shortness of breath, and cognitive dysfunction as well as others that generally impact an individuals' everyday functioning.

Outcome measures

A composite adverse maternal outcome was defined as the presence of any of the following: early pregnancy loss, preterm birth, GDM, and GHTN/PET. Similarly, a composite adverse neonatal outcome was defined as the

presence of any of the following: neonatal intensive care unit (NICU) admission, small for gestational age (SGA), congenital anomalies, and neonatal death. The incidence of long COVID was also calculated.

Statistical analysis

Data were analyzed using IBM SPSS Statistics, version 26.0 statistical software (IBM Corp., Armonk, NY, USA). Categorical variables are expressed as numbers (frequency). Fisher's exact test or Pearson's chi-squared test was used to compare categorical variables. For continuous variables, QQ plots were used to confirm normal distribution, Levene's test was used to examine the equality of variances and an independent t-test or analysis of variance was used to compare variables among the groups. Statistical significance was assumed at values of $p \leq 0.05$.

Results

Ninety pregnant women contracted SARS-CoV-2 during the study period. Of them, 13 developed warning symptoms that warranted referral to a central public hospital for further care and management without the ability to access reliable and official information related to disease progression or pregnancy outcome. Five others declined to participate in the study; hence, 72 who contracted COVID-19 and did not require hospitalization were included in the final analysis (Figure 1). This cohort comprised one twin pregnancy and 71 singleton pregnancies. The mean maternal age was 28.5 ± 4.7 years, the mean body mass index was 27.8 ± 5.2 kg/m2; 43.1% were primiparas, while 26.4% were smokers. Twelve women (16.7%) had comorbidities: thyroid disorders in six, anemia in three, diabetes mellitus in one, familial Mediterranean fever in one, and renal disease in one. Twenty women (27.8%) contracted the infection during the first trimester, 31 (43.1%) during the second trimester, and 21 (29.1%) during the third trimester. The mean gestational age at the positive RT-PCR result was 21.0 ± 10.0 weeks, mean infection duration was 17.0 ± 8.3 days, mean infection to delivery interval was 15.3 ± 10.1 weeks and mean gestational age at delivery was 38.0 ± 1.7 weeks. Twenty-nine women (40.3%) were asymptomatic at the time of the RT-PCR, three (4.2%) contracted another COVID-19 infection during the index pregnancy, and 12 (16.7%) received the COVID-19 vaccination (Table 1). The most common presenting complaints among the 43 symptomatic women were fatigue, fever, and myalgia. The frequencies of these and other symptoms are shown in Figure 2.

Table 1. Baseline characteristics of the study population.

Population, n	72
Maternal age, years	28.5 ± 4.7
Primiparity	31 (43.1%)
Smoker	19 (26.4%)
BMI, kg/m²	27.8 ± 5.2
Gestational age at infection, weeks	21.0 ± 10.0
Gestational age at delivery, weeks	38.0 ± 1.74
Infection duration, days	17.0 ± 8.3
Infection-delivery interval, weeks	15.3 ± 10.1
Asymptomatic	29 (40.3%)
Second COVID-19 infection	3 (4.2%)
COVID-19 vaccine received	12 (16.7%)
Comorbidities (thyroid disorder, anemia, diabetes mellitus, familial Mediterranean fever, renal disease)	12 (16.7%)

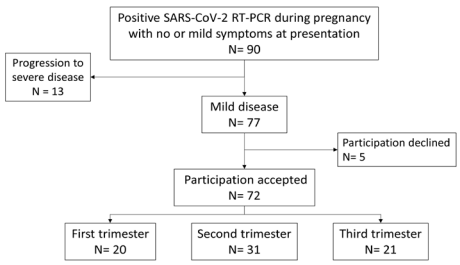

Fig. 1 Flowchart of the study population selection. Abbreviations: RT-PCR: reverse transcription polymerase chain reaction, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

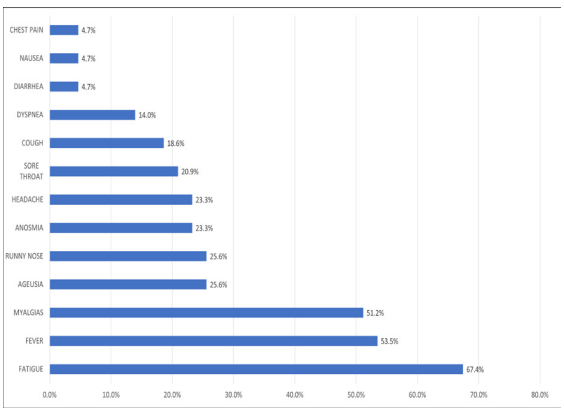

Fig. 2 Symptoms at the initial presentation of the 43 pregnant women with mild Novel-Covid-19.

Four women experienced early pregnancy failure. The first woman had a positive RT-PCR result at 8 WG and a failed pregnancy at 12 WG. The second patient had a positive RT-PCR result at 7 WG and a failed pregnancy at 11+6/7 WG. The third woman had a positive RT-PCR result at 4 WG and a failed pregnancy at 5 WG. The fourth woman had a positive RT-PCR result at 11 WG and a failed pregnancy at 12+6/7 WG. Five cases of preterm birth were encountered: four after spontaneous labor and one due to severe bleeding instigated by placenta previa at 29 WG. Three women developed GDM, one developed PET, and one developed GHTN. There were no cases of preterm rupture of membranes, chorioamnionitis, abruptio placentae, thromboembolism, or postpartum hemorrhage.

Three infants were SGA (4.3%), while one was born with a congenital heart anomaly. Seven infants were admitted to the NICU: three with transient tachypnea of the newborn, two with respiratory distress syndrome, and two with suspected sepsis (vomiting and hypoglycemia). One case of early neonatal death was documented in an asymptomatic woman. The mother contracted the infection at 21 WG and delivered at 33+4/7 WG. A 1300 g infant was delivered by cesarean delivery following preterm labor with 1- and 5-min Apgar scores of 6 and 7, respectively. The patient developed ARDS followed by disseminated intravascular coagulopathy and multiorgan failure and ultimately died. Multisystem inflammatory syndrome was suspected in this neonate. There were no cases of stillbirth or neonatal asphyxia.

Long COVID was identified in 34 (47.2%) women; the frequency of the symptoms is shown in Figure 3. We could not elicit any statistically significant influence of the presence versus the absence of symptoms on RT-PCR test results (symptomatic versus asymptomatic) on illness course or composite adverse maternal or neonatal outcomes (Table 2). Similarly, the timing of infection during pregnancy exerted no significant effect on the illness or the two composite outcomes (Table 3).

Table 2. Comparison of outcomes between symptomatic and asymptomatic patients at the time of RT-PCR-testing.

Outcome	Total n= 72	Symptomatic n= 43	Asymptomatic n= 29	p value
Infection-Delivery Interval, weeks	15.3 ± 10.1	15.8 ± 9.8	16.6 ± 10.2	0.583
Infection duration, days	17.0 ± 8.3	16.3 ± 7.2	17.7 ± 5.7	0.433
Composite adverse maternal outcomes	14 (19.4%)	6 (14.0%)	8 (27.6%)	0.152
Composite adverse neonatal outcomes	9 (12.5%)	3 (7.0%)	6 (20.7%)	0.084
Cesarean delivery	42/68 (61.8%)	26 (65.0%)	16 (57.1%)	0.512
Gestational age at delivery, weeks	38.1 ± 1.7	38.4 ± 1.1	37.6 ± 2.3	0.056
Long-COVID	34 (47.2%)	23 (53.5%)	11 (37.9%)	0.195

Table 3. Comparison of outcomes among the trimesters at the time of RT-PCR-testing.

Outcome	First trimester n= 20	Second trimester n= 31	Third trimester n= 21	p-value
Asymptomatic infection	8 (40.0%)	12 (38.7%)	9 (42.9%)	0.956
Infection duration, days	17.8 ± 9.4	17.5 ± 6.1	15.1 ± 4.4	0.377
Composite adverse maternal outcomes	5 (25.0%)	5 (16.1%)	4 (19.0%)	0.736
Composite adverse neonatal outcomes	2 (10.0%)	5 (16.1%)	2 (9.5%)	0.720
Cesarean delivery	9 (56.3%)	19 (61.3%)	14 (66.7%)	0.810
Gestational age at delivery, weeks	38.6 ± 0.9	37.8 ± 2.2	38.1 ± 1.4	0.284
Long-COVID	9 (45.0%)	13 (41.9%)	12 (57.1%)	0.544

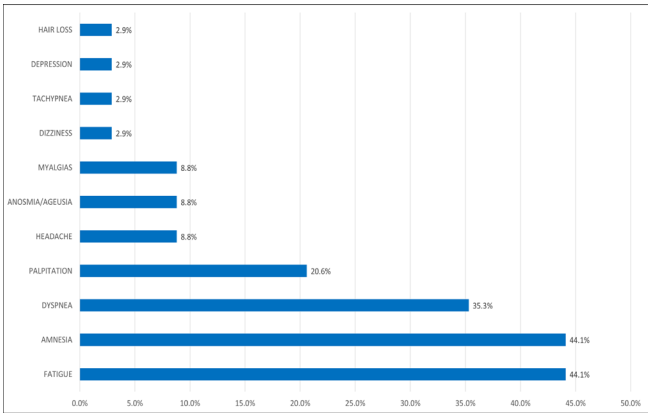

Fig. 3 Symptoms related to long-COVID syndrome in the study population.

Discussion

This study aimed to assess the medical course and pregnancy outcomes of women with mild COVID-19. The composite rates of adverse maternal and neonatal outcomes in this cohort were 19.4% and 12.5%, respectively. The incidence of long COVID was 47.2%. These incidences did not vary significantly neither according to the symptomatic versus the asymptomatic status of the patient nor according to the trimester during which the infection was contracted.

In our study population, 40.27% were asymptomatic, and the only indication for the RT-PCR testing was a history of exposure to an infected individual. This rate was higher than the 12.1% reported in a quarantined group of both sexes with mild COVID-19.[12] The commonest presenting symptoms observed among symptomatic women were fatigue, myalgia, and fever, as contrasted to individuals with mild disease in the general population, who presented with fatigue, headache, and cough.[12]

Another study that recruited a mixed population from one isolation center reported that 19.1% of their cohort with mild COVID-19 infection was asymptomatic.[13] In several maternities in the Kingdom of Saudi Arabia (KSA), 4.2% of women tested positive for COVID-19 and 62% were asymptomatic.[14] The high rate observed in our study confirms the observation of a higher rate of asymptomatic cases during pregnancy.[15]

Being asymptomatic at RT-PCR testing does not exclude the possibility of future symptoms or a more severe form of the infection. In fact, 13 of 90 (14.4%) patients in this cohort experienced symptoms that mandated admission to a different designated hospital for care and management. Unfortunately, no information concerning the course of their disease or pregnancy outcomes was available to us. In the series described by Breslin et al., eight of 12 asymptomatic infected pregnant women developed symptoms, while four remained asymptomatic .[16]

The importance of the initial symptoms during RT-PCR testing in predicting disease severity is not fully understood. It has been suggested that dyspnea might predict severe disease and intensive care unit admission;[17] however, it remains controversial in severe illness despite a lack of evidence to support its predictive value in mild disease. Nonetheless, in mild illness, whether during or outside pregnancy, no studies to date have identified the significance of any particular symptom in predicting progression to severe illness.

The mild clinical form of COVID-19 constitutes the majority of all cases; however, most published literature has focused on describing the course and outcome of severe and critical cases among hospitalized patients during and outside pregnancy. Early reports released by the United States Centers for Disease Control and Prevention considered pregnancy and puerperium risk factors for infection.[18] Another more alarming statement supported an increased risk of severe illness among pregnant versus age-matched non-pregnant patients, including the increased need for hospitalization, intensive care unit admission, and respiratory support with ventilation.[4,5] Consequently, such disturbing information instigated panic among women.[19] Despite the low incidence of vertical transmission, an unknown percentage of women with COVID-19 elected to terminate their early pregnancies.[20]

In this study, the incidence of early pregnancy failure was 20% among the women infected during the first trimester. This observation was in accordance with a study by Cavalcante et al., who reported an early pregnancy loss rate of 23.1%, which was considered within the normal range of the general obstetric population. The same review concluded that infection during the first trimester of pregnancy does not predispose women to early pregnancy loss.[21]

Early reports recognized an association between COVID-19 during pregnancy and adverse maternal and neonatal outcomes [4]; however, this probably applies only to a minority of pregnant women who develop severe or critical COVID-19. Most pregnant individuals who develop COVID-19 sustain a mild/asymptomatic form of the disease. Increasing evidence links the mild clinical form during pregnancy to a normal pregnancy outcome. In a study by Brandt et al., which included women with both mild and severe forms of COVID-19, severe infection

was associated with more adverse obstetrical outcomes, whereas mild disease cases had obstetrical outcomes similar to those of controls.[22]

Moreover, despite a possible association between worse pregnancy outcomes and contracting the infection beyond 20 WG,[23] we did not observe a difference in the natural history of the illness itself, such as the duration of infection, infection to delivery interval, or maternal–fetal outcomes with respect to infection timing. This association is probably limited to severe and critical forms of the disease. Another explanation could be related to the small sample size, which did not provide sufficient power to show such an association.

Some patients may have persistent symptoms for weeks or months following SARS-CoV-2 infection, a condition termed long or extended COVID. Symptoms may appear following the initial recovery from an acute COVID-19 episode or persist from the initial SARS-CoV-2 infection .[11] Risk factors for this condition are unclear; however, irrespective of the severity of the initial infection, any convalescent individual can develop this condition, although it is more likely to follow a severe illness. The incidence of long COVID is estimated at 10–35%, while for hospitalized patients, it may reach 85%.[24] In this cohort, long COVID affected 47.2% of the convalescent women. The most frequent symptoms were fatigue, amnesia, and dyspnea.

This study confirmed the mild nature and favorable outcomes of mild infection during pregnancy.[25] However, there is currently no exact method of predicting which patients will continue to have only a mild infection or will develop a severe or critical form. Nevertheless, we can confidently counsel pregnant women that home self-isolation is safe, and that mild illness is the most probable course (91%), although more severe illness is possible. It is prudent to practice a high degree of protective measures such as vaccination, physical distancing, and the proper use of masks in closed areas. However, the antenatal visit schedule should not be modified. In cases of infection, antenatal visits should not be canceled but rather safely achieved via telemedicine, videoconferencing, or home visits by dedicated and specialized healthcare workers .[26] This methodology during isolation at home or at quarantine centers is intended to curb the spread of this highly contagious disease, monitor its progression, and ensure the well-being of the mother and fetus.

Long-term longitudinal studies could examine the impact of mild versus severe COVID-19 on maternal outcomes such as the persistence of long COVID as well as the development of infants during the first few years of life.

This study is one of the few to report the medical course and pregnancy outcomes of women with mild infection who remained at home in self-isolation and did not require hospital admission and constituted the largest proportion of the obstetric population. Moreover, this series reported the outcomes of cases contracted during the first trimester, whereas in earlier studies, delivery was performed within 2 weeks for fear of teratogenicity. In our cohort, no pregnancy terminations were attempted despite the inclusion of 20 first-trimester cases, probably due to cultural reasons. This allowed for the assessment of the impact of infection during early pregnancy. This prospective study examined short- and mid-term outcomes and was conducted in a population that has not been well studied in a region in serious economic crisis with limited access to healthcare facilities.

The limitations of this study were its small sample size and similar to other single-center studies, the inherent lack of generalizability of our findings. Although screening for vertical transmission was not part of the study's protocol, the suspicion of neonatal sepsis instigated a complete sepsis workup including SARS-CoV-2 RT-PCR and immunoglobulins in the newborn.

Conclusion

Asymptomatic or mild COVID-19 may not be associated with adverse maternal or neonatal outcomes; however, predicting disease progression is difficult. Moreover, long COVID is relatively common and should be investigated further in future studies.

Conflicts of Interest: No conflicts declared.

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