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CLINICAL ARTICLE

Obstetrics

Should pregnant women be screened for SARS-CoV-2 infection? A prospective multicenter cohort study

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Abstract

Objective: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), ranges from asymptomatic to severe infection. We aimed to compare the prevalence of COVID-19 in asymptomatic pregnant versus nonpregnant women in order to establish recommendations for a COVID-19 screening strategy.

Methods: A prospective multicenter cohort study was conducted. Asymptomatic pregnant or nonpregnant women after March 2020 (the time when COVID-19 was first detected in north Israel) were tested for SARS-CoV-2 using nasopharyngeal reverse transcription polymerase chain reaction test, anti-nucleocapsid IgG, and anti-spike IgG. Diagnosis was made if at least one test result was positive. Pregnant women were tested between 34 and 42 weeks, mostly at birth.

Results: Among the 297 participating women, 152 were pregnant and 145 were nonpregnant. The prevalence of asymptomatic COVID-19 was similar between the groups (4 [2.6%] and 8 [5.5%], respectively; $P = 0.2$). All women with COVID-19 delivered healthy appropriate-for-gestational-age babies without malformations, at term.

Conclusions: The rate of asymptomatic COVID-19 in pregnant women is low and comparable to the rate among nonpregnant women. Pregnancy outcomes are favorable. Future screening programs should consider that one of 25 screened asymptomatic women will be positive.

KEYWORDS
COVID-19, pregnancy, SARS-CoV-2, screening

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an RNA virus and the pathogen of coronavirus disease 2019 (COVID-19). The disease can range from asymptomatic infection to severe illness and death.[1-7] Diagnosis of SARS-CoV-2 infection is based on reverse transcription polymerase chain reaction (RT-PCR) performed on nasopharyngeal samples.[8] Serologic tests are also used to detect past and present SARS-CoV-2 infection; anti-spike IgG and IgM and anti-nucleocapsid IgG detection kits are commercially available.

Enav Yefet and Manal Massalha contributed equally to this work.

The effect of pregnancy on COVID-19 manifestations includes higher rates of admission to the intensive care unit, need for mechanical ventilation, extracorporeal membrane oxygenation, and death in pregnant women compared with nonpregnant individuals. Increased risk for preterm birth and pre-eclampsia following maternal SARS-CoV-2 infection were also reported.[1–7]

Pregnancy is a state of relative immunosuppression, in which the feto-protective dominance of the T-helper 2 system, particularly in the second trimester, may leave the mother susceptible to viral infections, which are more effectively contained by the T-helper 1 system. Thus, maternal immune response may be attenuated, which may subsequently lead to an increased rate of asymptomatic infection.[9,10]

Previous studies have provided data regarding the rate of SARS-CoV-2 infection among asymptomatic pregnant women.[11–19] Comparison with a control group of nonpregnant women has not been conducted. Elucidating the true rate of asymptomatic infection in pregnant women is important for monitoring possible pregnancy complications and vertical transmission and for preventing additional viral spreading. It is also important for public health issues, including the decision of whether to screen asymptomatic pregnant women for SARS-CoV-2 infection.

SARS-CoV-2 infection was first detected in north Israel in March 2020. The following months represent a period when women were either pregnant or nonpregnant from the time the pandemic broke out. Thus, the asymptomatic infection rate could be evaluated without concern for crossover between the groups.

The present study aimed to examine the rate of asymptomatic infection among pregnant and nonpregnant women as well as pregnancy outcomes following asymptomatic maternal infection.

2 | MATERIALS AND METHODS

2.1 | Design

This multicenter prospective cohort study was conducted between July 14, 2020, and February 3, 2021, at Baruch-Padeh and Emek Medical Centers, two university teaching medical centers in north Israel. The study protocol was approved by their institutional review boards (51-20-POR and 61-20-EMC). Informed consent was obtained from all individuals who participated in the study.

The study cohort consisted of women between 18 and 50 years of age who were either pregnant or not pregnant after March 16, 2020, when the first patient with COVID-19 was diagnosed in north Israel, until February 3, 2021. Pregnant women were recruited if their last menstrual period was before March 2, 2020 (March 2, 2020, was chosen as the last menstrual period since it is 14 days before March 16, 2020) to make sure that they were pregnant throughout the COVID-19 pandemic. Nonpregnant women were recruited if they were not pregnant during the same period. Women with typical COVID-19 symptoms at any time during the pandemic were excluded. No women were vaccinated during the study period.

Pregnant women were recruited before or immediately after delivery. Nonpregnant women were recruited at the fertility units, gynecology wards, and emergency departments of the participating medical centers. In addition, eleven women from the staff personnel who performed serology tests for screening purposes were recruited as well.

After enrollment, SARS-CoV-2 PCR was performed on nasopharyngeal swabs and serum anti-nucleocapsid IgG and anti-spike IgG were measured.

2.2 | SARS-CoV-2 antibodies determination

SARS-CoV-2 antibodies were determined using ready-to-use assays on automated analyzers according to the manufacturer's instructions (Table 1). More specifically, serum was separated from clot and blood cells by centrifugation (1000 *g*, 10 min) using gel separator tubes. Samples were either directly tested on the day of collection for SARS-CoV-2 anti-nucleocapsid IgG antibodies using an Architect i2000 analyzer (Abbott) or were separated into a secondary tube and frozen at −20°C until the test was performed. After performing the test, samples were frozen at −20°C. For SARS-CoV-2 anti-spike (S1/S2) IgG antibodies determination, samples were thawed and

TABLE 1 Anti-SARS-CoV-2 antibody detection assays

Kit no.	Trade name	Measured analyte	Assay manufacturer	Method	Analyzer	Cutoff	Clinical performance (>15 days after positive PCR result)
1	SARS-CoV-2 IgG	SARS-CoV-2 nucleocapsid IgG antibodies	Abbott Diagnostics, Sligo, Ireland	Chemiluminescence microparticle immunoassay	Architect i2000R	1.4 index (sample/cutoff)	Sensitivity 100.0% Specificity 99.6%
2	Liaison SARS-CoV-2 S1/S2 IgG	SARS-CoV-2 IgG anti-S1 and anti-S2 antibodies	DiaSorin S.p.A., Saluggia, Italy	Chemiluminescence immunoassay	Liaison XL	12.0 AU/ml	Sensitivity 97.4% Specificity 98.5%

Abbreviations: PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

mixed by vortex and antibody presence was detected using a Liaison analyzer (DiaSorin).

2.3 | Outcome measures

The primary outcome was the rate of women with SARS-CoV-2 infection (either positive nasopharyngeal PCR or serology). Secondary outcomes were pregnancy outcomes of pregnant women with SARS-CoV-2 infection during pregnancy.

3 | SAMPLE SIZE

3.1 | Statistical analysis

Assuming that the rates of asymptomatic SARS-CoV-2 infection in the general population and during pregnancy are 5% and 15%, respectively, 282 women were required (300 women with dropouts; 5% two-sided α, 80% power).

Categorical variables were compared among groups using χ^2 test or Fisher exact test. For continuous variables, *t* test (or Wilcoxon two-sample test) was implemented. Differences in group characteristics were adjusted using multivariable logistic regression.

Statistical analyses were performed with SAS version 9.4 (SAS Institute Inc). Significance was set at a *P* value of <0.05.

4 | RESULTS

Among the 297 participating women, 152 were pregnant and 145 were nonpregnant during the study period. Group characteristics are presented in Table 2. Pregnant women were younger, had more children at home, were less likely to be of Jewish ethnicity, and were more likely to be religious (Table 2). The prevalence of asymptomatic SARS-CoV-2 infection was similar between pregnant and nonpregnant women (4 [2.6%] and 8 [5.5%], respectively; $P = 0.2$) (Table 3). The prevalence of asymptomatic SARS-CoV-2 infection remained statistically insignificant after adjusting unbalanced background characteristics (ethnicity, likelihood of being religious, maternal age, and number of children at home) (Table 4).

All women with SARS-CoV-2 during pregnancy delivered healthy, appropriate-for-gestational-age babies, at term, without malformations (Table 5).

TABLE 2 Patient characteristics

Parameter	Pregnant (*n* = 152)	Nonpregnant (*n* = 145)	*P* value
Age, years	29.8 (5.4) [29.5, 26–33]	35.4 (7.1) [35, 30–41]	<0.0001
BMI, kg/m^2	24.7 (4.6) [23.6, 22–27.3]	26 (5.2) [24.9, 22–29.3]	0.08
Years of education[a]	14.3 (2.6) [12–16]	14.3 (2.7) [12–16]	0.97
No. of children	1.4 (1.6) [1.0–2]	1.2 (1.5) [1, 0–2]	0.15
No. of children at home	1.4 (1.6) [1.0–2]	1.1 (1.4) [1, 0–2]	0.03
Ethnicity (Jewish)	84 (55%)	102 (70%)	0.007
Religious	111 (73%)	77 (53%)	0.0005
Nonreligious	41 (27%)	67 (47%)	
Place of residency			0.13
City ≥ 20,000	73 (48%)	57 (39%)	
Village < 20,000	79 (52%)	88 (61%)	

Note: Values are presented as mean (standard deviation) [median, interquartile range] or number (percentage).Eleven women were staff members. All of them belonged to the nonpregnant group and all were negative for severe acute respiratory syndrome coronavirus 2 infection.

Abbreviation: BMI, body mass index.

[a]From first grade.

TABLE 3 Asymptomatic SARS-CoV-2 infection rates in pregnant and nonpregnant women

Parameter	Pregnant (*n* = 152)	Nonpregnant (*n* = 145)	*P* value
Positive PCR (nasopharyngeal swab)	1 (0.7%)	1 (0.7%)	1
Positive serology (blood test)	3 (2%)	7 (4.8%)	0.2
Total tests positive for SARS-CoV-2	4 (2.6%)	8 (5.5%)	0.2

Note: Values are presented as number (percentage).In the pregnant women group, both severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleocapsid IgG and anti-S1/S2 IgG antibodies were positive. In the nonpregnant group, three women had positive SARS-CoV-2 nucleocapsid IgG antibodies and four women had both types of antibodies.

Abbreviation: PCR, polymerase chain reaction.

5 | DISCUSSION

The present study aimed to compare the rate of asymptomatic SARS-CoV-2 infection in pregnant versus nonpregnant women. The overall rate of asymptomatic infection was 4%, without a significant difference between the cohorts. This rate aligned with the previously reported 2% to 8% prevalence rates of asymptomatic or mild symptomatic SARS-CoV-2 infections in pregnant women[11-19]; however, a control group of nonpregnant women was not included in those studies.

Dawood et al. prospectively followed a cohort of pregnant women who self-collected midturbinate nasal swabs for SARS-CoV-2 RT-PCR testing once weekly for approximately 10 weeks. The rate of SARS-CoV-2 infection was 5.7 per 1000 (95% confidence interval [CI], 1.7–9.7) for symptomatic infections and 3.5 per 1000 (95% CI, 0–7.1) for asymptomatic infections.[12] A control group of nonpregnant women was not evaluated and serology tests were not performed.

The risk for SARS-CoV-2 transmission in asymptomatic infection is a major public health concern. A recent meta-analysis of 79 studies that addressed this question in the general population estimated that 20% of people who become infected with SARS-CoV-2 remained asymptomatic throughout infection (95% CI, 17–25), with a prediction interval of 3% to 67%. The relative risk for secondary attack rate in contacts of people with asymptomatic infection compared with those with symptomatic infection was 0.35 (95% CI, 0.10–1.27).[20] The authors raised concerns that there was an overrepresentation of participants diagnosed because of symptoms, and potential selection biases in screening studies that might have overestimated the proportion of asymptomatic infections. To estimate the true proportion of asymptomatic infections, there is a need to design prospective longitudinal studies with clear definitions and methods that minimize selection and measurement biases, using serological tests, in combination with virological diagnostic methods.[20] In the present study, these suggestions were implemented by using a prospective design with recruitment of all potential suitable participants at the same time and location, to minimize selection bias with adjustments for background differences. Serological tests, in combination with RT-PCR, were used and a comparison group of nonpregnant women was included.

In a study that examined the presence of anti-spike IgG following asymptomatic, mild and severe COVID-19 in a cohort of 1884 healthcare workers and 51 hospitalized COVID-19 patients, the majority of anti-spike IgG-positive individuals remained IgG-positive for at least 8 months regardless of initial COVID-19 disease severity. The presence of anti-spike IgG antibodies was associated with a substantially reduced risk of reinfection up to 9 months following asymptomatic to mild COVID-19.[21] These data suggest that the low rate of positive serology found in our study reflects a low rate of asymptomatic infection in the population and not antibody disappearance over time. Supporting evidence that the rates of asymptomatic carriage is low was previously demonstrated by studies that have shown that the IgG levels were also low and would have stayed elevated for several months after infection although the precise duration was unknown.[22,23] In addition, some patients with PCR-proven COVID-19 may remain seronegative.[23]

The strengths of this study are its multicenter prospective design, combined use of serology and RT-PCR tests, recruitment of women of childbearing age from a similar geographical area at the same period, and controlling for background characteristics with a potential effect on the study end points. The use of a control group of nonpregnant women in order to evaluate the effect of pregnancy on asymptomatic infection and the use of the critical time point when women were pregnant or nonpregnant throughout the entire time from the pandemic breakout are also strengths of the study. The limitations of the study are control-group enrollment of women at the medical center fertility units, gynecology wards, and emergency departments and staff personnel. However, these women are not considered to be at higher risk for infection and therefore likely represent the infection rate in the general population. Another limitation is the small number of neonates born to mothers with

TABLE 4 Asymptomatic SARS-CoV-2 infection rates: multivariable analysis

Parameter	Odds ratio (95% confidence interval)
Pregnant vs. nonpregnant	0.51 (0.13–2.0)
Ethnicity	1.33 (0.32–5.55)
Religious	1.72 (0.4–7.43)
Age	1.03 (0.94–1.13)
No. of children at home	1 (0.7–1.5)

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

TABLE 5 Delivery and neonate characteristics among pregnant women with SARS-CoV-2 infection

Case	Delivery week (week + days)	Mode of delivery	Birth weight (g)	Neonate sex	APGAR at 1 min	APGAR at 5 min	Cord-pH
1	40 + 3	Cesarean delivery because of failed vacuum for nonreassuring fetal heart rate monitoring	3320	Female	9	9	7.24
2	39 + 4	Vacuum for non-reassuring fetal heart rate monitoring	3670	Male	8	9	7.29
3	38 + 5	Partus spontaneous	3020	Female	9	10	7.33
4	37 + 1	Partus spontaneous	3700	Male	9	10	7.3

COVID-19, which limited the ability to draw conclusions regarding pregnancy outcomes. The study design introduces the risk that the prevalence of COVID-19 could have been influenced by epidemiologic changes that occurred over the time frame of the study. A cross-sectional study design over a shorter time frame would have solved this limitation; however, such a study was impractical because of the lack of enough patients.

6 | CONCLUSIONS

The rate of asymptomatic COVID-19 in pregnant women is low and comparable to the rate among nonpregnant women, with one in 25 women testing positive. In infected women, pregnancy outcomes are favorable.

AUTHOR CONTRIBUTIONS

E.Y., M.M., A.A., A.G.H., S.H.M., L.N., M.W., J.S., S.B., A.W., R.I., A.P., O.R., J.S.Y., Y.P., and Z.N. participated in the study design and data collection. E.Y. and Z.N. analyzed the data and wrote the manuscript. M.M., A.A., A.G.H., S.H.M., L.N., M.W., J.S., S.B., A.W., R.I., A.P., O.R., J.S.Y., and Y.P. critically reviewed the manuscript.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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