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RESEARCH ARTICLE

COVID-19 symptoms and antibody positivity among unvaccinated pregnant women: An observational study in seven countries from the Global Network

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Abstract

Objective: To determine the relation of COVID-19 symptoms to COVID-19 antibody positivity among unvaccinated pregnant women in low- and middle-income countries (LMIC).

Design: COVID-19 infection status measured by antibody positivity at delivery was compared with the symptoms of COVID-19 in the current pregnancy in a prospective, observational cohort study in seven LMICs.

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Setting: The study was conducted among women in the Global Network for Women's and Children's Health's Maternal and Newborn Health Registry (MNHR), a prospective, population-based study in Kenya, Zambia, the Democratic Republic of the Congo (DRC), Bangladesh, Pakistan, India (Belagavi and Nagpur sites) and Guatemala.
Population: Pregnant women enrolled in the ongoing pregnancy registry at study sites.
Methods: Data on COVID-19 symptoms during the current pregnancy were collected by trained staff between October 2020 and June 2022. COVID-19 antibody testing was performed on samples collected at delivery. The relation between COVID-19 antibody positivity and symptoms was assessed using generalised linear models with a binomial distribution adjusting for site and symptoms.
Main outcome measures: COVID-19 antibody status and symptoms of COVID-19 among pregnant women.
Results: Among 19 218 non-vaccinated pregnant women who were evaluated, 14.1% of antibody-positive women had one or more symptoms compared with 13.4% in antibody-negative women. Overall, 85.3% of antibody-positive women reported no COVID-19 symptoms during the present pregnancy. Reported fever was significantly associated with antibody status (relative risk [RR] 1.10, 95% CI 1.03–11.18; $P = 0.008$). A multiple variable model adjusting for site and all eight symptoms during pregnancy showed similar results (RR 1.13, 95% CI 1.04–1.23; $P = 0.012$). None of the other symptoms was significantly related to antibody positivity.
Conclusions: In a population-based cohort in LMICs, unvaccinated pregnant women who were antibody-positive had slightly more symptoms during their pregnancy and a small but significantly greater increase in fever. However, for prevalence studies, evaluating COVID-19-related symptoms does not appear to be useful in differentiating pregnant women who have had a COVID-19 infection.

KEYWORDS
COVID-19 antibody, COVID-19 symptoms, low- and middle-income countries, pregnant women

1 | INTRODUCTION

SARS-CoV-2 or COVID-19 infection has posed a significant burden to health care systems worldwide. More than 6 million people are believed to have died from this infection. Pregnancy and its outcomes have also been adversely affected by this infection.[1,2] There are many unknowns with respect to pregnant women and COVID-19 infection during the current pandemic.[3] One issue that needs attention is whether putative COVID-19 symptoms are useful in determining population rates of COVID-19 infections.

The Centers for Disease Control (CDC) has issued guidance regarding the potential symptoms related to COVID-19. Subsequently, the World Health Organization (WHO) also issued guidance on using symptoms to identify a COVID-19 infection.[4] However, varied presentation of symptoms of COVID-19 was observed during pregnancy in most of the published literature. These reports emphasised that most pregnant women infected with COVID-19 were relatively asymptomatic and were less likely to manifest COVID-19-related symptoms than were non-pregnant women.[5,6] A WHO systematic review of 11 observational studies suggested that of women of reproductive age who tested positive for COVID-19, a greater proportion of pregnant women were asymptomatic; when present, symptoms were also mild in nature.[7] Nevertheless, in a study of nearly 400 000 women of reproductive age with COVID-19, the CDC found that pregnant women had a greater risk for mortality and morbidity compared with non-pregnant women of reproductive age.[8] An issue with many of these studies is that they were not population-based, focusing on symptomatic women with the disease documented by the presence of antigens at the time of illness.

COVID-19 infection in pregnant women without classical presentation presents an added challenge regarding service provision, prevention and management. Additionally, there is a need to correlate the symptoms with the disease assessed by presence of COVID-19 antibodies. This paper presents the results pertaining to COVID-19 symptoms among pregnant women from our ongoing Maternal Newborn Health Registry (MNHR) population across seven low- and-middle income countries (LMICs) and investigated whether these symptoms were related to the infection status as measured by the presence of antibodies in the maternal serum.

2 | METHODS

This study was conducted by the Global Network for Women's and Children's Health Research (Global Network), a multi-country research network funded by the *Eunice Kennedy Shriver* National Institute of Child Health and

Human Development (NICHD).[9] The COVID-19 study among pregnant women was undertaken within the infrastructure of the ongoing Global Network's Maternal and Neonatal Health Registry (MNHR). The MNHR is a prospective, population-based observational study that includes all pregnant women, their newborns and their outcomes in defined geographical communities (clusters).[10,11] Each cluster includes approximately 300–500 births annually, with eight to ten clusters currently available at each of the Global Network sites in western Kenya, Zambia (Kafue and Chongwe), the Democratic Republic of the Congo (DRC) (North and South Ubangi Province), Pakistan (Thatta in Sindh Province), India (Belagavi and Nagpur), Guatemala (Chimaltenango) and Bangladesh (District Tangail). The MNHR has been ongoing in all sites since 2008, except for the DRC, which joined in 2014, and the Bangladesh site, which joined in 2018.

Trained study healthcare staff (registry administrators [RAs]) identified pregnant women in their respective clusters. Following informed consent, these women were enrolled in the MNHR.[10,11] The RAs obtained basic health and demographic information at enrolment, and recorded the date of the last menstrual period (LMP) and/or early ultrasound report to assess gestational age (GA). Maternal height, weight and haemoglobin were also documented. The next visit was carried out following delivery of the women to collect information on pregnancy outcomes as well as healthcare received during delivery. The maternal and newborn health status was collected at 42 days post-delivery. The outcomes were based on the review of medical records and birth attendant and family interviews. During the active phase of the pandemic, the study staff often collected the information by telephone or by home visits using the necessary precautions.

The pregnant women enrolled in the MNHR reconsented to participate in the COVID-19 study, as this involved collection of additional information and samples for antibody assessments. The timing of the COVID-19 study initiation varied by site (beginning in October 2020 for Pakistan; in November 2020 for Bangladesh, Guatemala, Nagpur and India; in December 2020 in Kenya and Belagavi India; and in February 2021 in Zambia) and the data collection continued until the end of June 2022 across all the study sites. As we did not have the resources to perform antibody testing on all women delivering, we asked each site to collect a blood sample on a maximum of 170 women per month. Some sites collected fewer samples. At the time of the blood sample collection, a questionnaire was administered asking about potential COVID-19-related symptoms before the pregnancy, during the pregnancy, and at the time of the sample collection (for this study we present responses related to the current pregnancy). The maternal serum sample was generally collected at delivery; however, a 2-week window for antibody collection was allowed by protocol. The antibody test results for the samples collected in the Global Network sites were analysed and linked to data in the MNHR. The assay was performed by laboratory staff at each of the sites as per the manufacturer's protocol with quality oversight by the Research Triangle Institute (RTI), USA staff.[12]

Symptoms of COVID-19 infection included fever, cough, shortness of breath or breathing difficulty, chills, muscle pain, headache, sore throat and loss of taste or smell, based on the WHO criteria.[13] Mothers who received one or more doses of COVID-19 vaccine were documented. This analysis was undertaken among women had never received any type of COVID-19 vaccine.

2.1 | Statistical analysis

Pregnant women who delivered at ≥20 weeks of gestation, had not received a COVID-19 vaccination, and provided a serum sample at delivery with a COVID-19 antibody test completed were included in this analysis. Maternal demographic characteristics, antibody positivity and COVID-19 symptoms during pregnancy are presented with frequencies and percentages. To assess the relation between COVID-19 symptoms among unvaccinated pregnant women and antibody positivity, relative risks (RR) and 95% confidence intervals (CI) were obtained from generalised linear models with terms for site and symptom with a separate log binomial model for each COVID-19 symptom. Additionally, relative risks and 95% confidence intervals were obtained from a multivariable generalised linear model adjusting for site and all eight COVID-19 symptoms reported during pregnancy. All analyses were conducted in SAS v. 9.4 (SAS Institute).

2.2 | Ethical considerations

This study was reviewed and approved by the ethics review committees of all participating sites: INCAP, Guatemala; University of Zambia, Zambia; Moi University, Kenya; Aga Khan University, Pakistan; KLE Academy of Higher Education and Research's Jawaharlal Nehru Medical College, Belagavi, India; Lata Medical Research Foundation, Nagpur, India; Kinshasa School of Public Health, Democratic Republic of the Congo; and the International Centre for Diarrhoeal Disease Research, Bangladesh. The Institutional Review Boards at each US partner university and the Data Coordinating Centre (RTI International) also approved the protocol. All women provided informed consent for participation in the study, the data and sample collection.

3 | RESULTS

Across all the GN sites, from October 2020 to June 2022, 54 400 pregnant women were screened and 50 424 women had pregnancy outcomes ≥20 weeks of gestation. A serum sample was obtained from 22 888 women at delivery and antibody results were available for 22 241 participants. Figure 1 summarises the study enrolment. A total of 19 218 of these

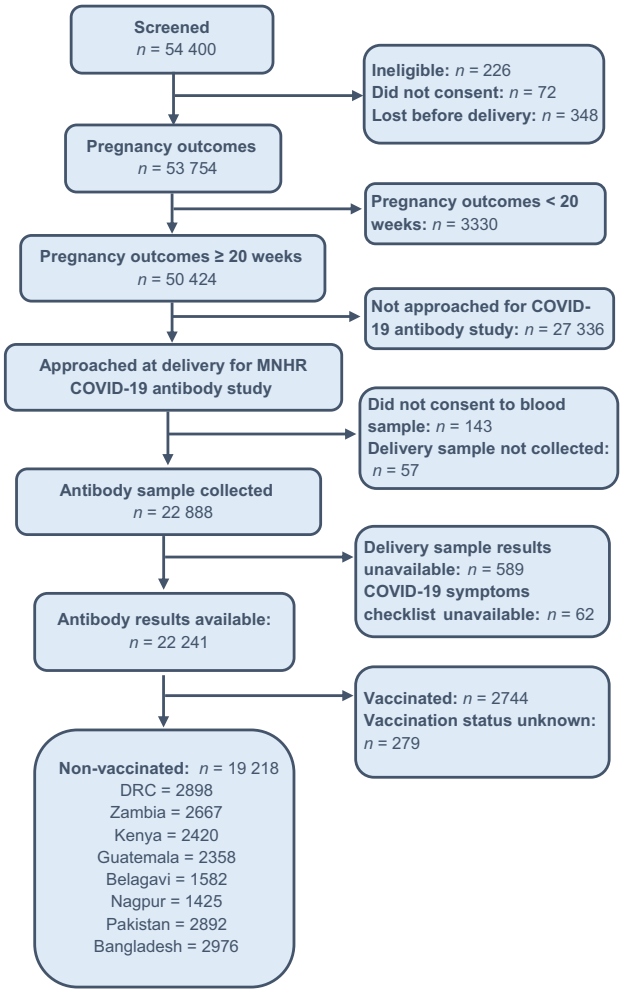

FIGURE 1 Enrolment in the Global Network COVID-19 antibody study.

TABLE 1 Comparison of the maternal characteristics of all women with available COVID-19 results with the characteristics of non-vaccinated women who had available COVID-19 results.

Variable	Women with available COVID-19 antibody results, *n* = 22 241 (%)	Non-vaccinated women with COVID-19 antibody results available, *n* = 19 218 (%)
Education	22 236	19 213
No schooling	4388 (19.7)	4094 (21.3)
1–6 years	4300 (19.3)	3834 (20.0)
7–12 years	11 893 (53.5)	10 035 (52.2)
≥13 years	1655 (7.4)	1250 (6.5)
Age (years)	22 239	19 216
<20	3520 (15.8)	3222 (16.8)
20–35	17 446 (78.4)	14 835 (77.2)
>35	1273 (5.7)	1159 (6.0)
Parity	22 240	19 217
0	7260 (32.6)	6094 (31.7)
1–2	9779 (44.0)	8346 (43.4)
>2	5201 (23.4)	4777 (24.9)
Delivery location	22 241	19 218
Facility	18 839 (84.7)	16 113 (83.8)
Home/other	3402 (15.3)	3105 (16.2)
ANC visits	22 222	19 202
0	1368 (6.2)	1327 (6.9)
1	1375 (6.2)	1311 (6.8)
2	2308 (10.4)	2180 (11.4)
3	3862 (17.4)	3563 (18.6)
≥4	13 309 (59.9)	10 821 (56.4)

Abbreviations: ANC, ante natal care.

women were unvaccinated and these women constituted the analytical population for this study.

Table 1 presents the maternal characteristics of all participants with antibody assessments with known vaccination status in column 1. In column 2 are those with antibody assessments who were not vaccinated. The later 19 218 women are the study population. Overall, the maternal characteristics were similar in both groups.

Table 2 shows the proportion of non-vaccinated women overall and by site by antibody status. Among the non-vaccinated women, 34.3% were antibody-positive. The positivity rates ranged from 23.0% in Guatemala to 56.8% in Nagpur, India.

Table 3 shows the number and percentage of women overall and by site by antibody status with any COVID-19 symptoms and the number and percentage with one to three COVID-19 symptoms; 14.1% of antibody-positive women reported having one or more symptoms compared with 13.4% of antibody-negative women. The reported range in the percent of women reporting any symptoms was large, ranging from about 2% in Pakistan to about 32% in Bangladesh. However, the difference in symptoms between antibody-positive and antibody-negative women within the sites was generally small, and only in Belagavi did antibody-positive women have substantially more symptoms compared with antibody-negative women (24.3% versus 13.4%). Overall, 85.3% of antibody-positive women reported no COVID-19 symptoms during their pregnancy compared with 86.6% of antibody-negative women. Conversely, 14.7% of antibody-positive women versus 13.4% of antibody-negative women reported one or more symptoms. Slightly more antibody-positive women reported one symptom (8.4% versus 7.3%), similar numbers reported two symptoms (4.0% for each) and slightly more ≥3 symptoms (2.4% versus 2.1%) compared with antibody-negative women. The mean number of symptoms present also varied among the sites, but generally there were only small differences within the sites among those women who were antibody-positive and those who were antibody-negative.

We next looked at the individual symptoms among antibody-positive and antibody-negative women overall and by site (Table 4). Overall, fever was the most common symptom in both women with and without antibodies (7.8% versus

TABLE 2 COVID-19 antibody status at delivery in non-vaccinated women by study site.

Variable	Overall, *n* (%)	Democratic Republic of the Congo, *n* (%)	Zambia, *n* (%)	Kenya, *n* (%)	Guatemala, *n* (%)	India (Belagavi), *n* (%)	India (Nagpur), *n* (%)	Pakistan, *n* (%)	Bangladesh, *n* (%)
Antibody results in non-vaccinated women, *n* (%)	19 218	2898	2667	2420	2358	1582	1425	2892	2976
Positive	6584 (34.3)	1090 (37.6)	900 (33.7)	752 (31.1)	543 (23.0)	655 (41.4)	810 (56.8)	776 (26.8)	1058 (35.6)
Negative	12 146 (63.2)	1699 (58.6)	1744 (65.4)	1550 (64.0)	1762 (74.7)	889 (56.2)	569 (39.9)	2070 (71.6)	1863 (62.6)
Indeterminate	488 (2.5)	109 (3.8)	23 (0.9)	118 (4.9)	53 (2.2)	38 (2.4)	46 (3.2)	46 (1.6)	55 (1.8)

6.5%). Additionally, cough (5.1% versus 4.8%) and gastrointestinal symptoms such as vomiting and/or diarrhoea (5.4% versus 4.9%) were observed in slightly higher proportions among women with antibodies. Conversely, new onset loss of taste or smell was more common among women without antibodies. There were large differences in the reported rates of some of the symptoms among the sites, but there was little difference within the sites between women with and without antibodies.

The relation between antibody positivity and COVID-19 symptoms was assessed using generalised linear models with a binomial distribution adjusting for site and symptom (Table 5). Reported fever was significantly associated with antibody status with an RR of 1.10 (95% CI 1.03–11.18) ($P = 0.008$). A multiple variable model adjusting for site and all eight symptoms during pregnancy showed similar results. In this analysis, women with antibody positivity had an RR of fever of 1.13 (95% CI 1.04–1.23) ($P = 0.012$). None of the other symptoms were significantly related to antibody positivity.

4 | DISCUSSION

During the COVID-19 pandemic, many healthcare systems across the world used symptoms suggested by various professional organisations to define infection with COVID-19.[14] Clinical assessment of symptoms was used to determine the presence of COVID-19 disease in many resource-limited settings.[15] To determine the usefulness of symptoms in determining COVID-19 infections, we evaluated the relation between putative COVID-19 symptoms and COVID-19 antibody status among non-vaccinated pregnant women at delivery in eight sites in seven LMICs.

4.1 | Main findings

Across the Global Network sites over a period of 21 months (between October 2020 through June 2022), 22 241 pregnant women at ≥20 weeks of gestation who had provided a serum sample at delivery were evaluated. For this study, we specifically focused on the 19 218 women who were not vaccinated for COVID-19. Among these women, 6584 (34.3%) were positive for COVID-19 antibodies. We compared the potential symptoms of COVID-19 reported during the pregnancy and the results of antibody positivity. Overall, 14.7% of antibody-positive women had one or more symptoms compared with 13.4% of women who were antibody-negative. Although there were large differences in the rates of reported symptoms between the sites, within the sites there were only small differences in overall symptom rates between those with antibodies and those without antibodies. Similarly, although the individual sites had large differences in the rates of specific symptoms, within the sites there were only small differences in the rates of specific symptoms when antibody-positive and antibody-negative women were compared. To

TABLE 3 Symptoms potentially related to maternal COVID-19 infection During pregnancy among non-vaccinated women by COVID-19 antibody status at delivery and by site (*n* and %).

	Overall		Democratic Republic of the Congo		Zambia		Kenya
Variables	+	−	+	−	+	−	+
Delivery ≥20 weeks, *n* (%)	6584 (35.2)	12 146 (64.8)	1090 (39.1)	1699 (60.9)	900 (34.0)	1744 (66.0)	752 (32.7)
≥1 symptom during pregnancy, *n* (%)	969 (14.7)	1623 (13.4)	201 (18.4)	340 (20.0)	76 (8.4)	190 (10.9)	76 (10.1)
Number of symptoms during pregnancy, *n* (%)	6584	12 146	1090	1699	900	1744	752
Asymptomatic	5615 (85.3)	10 523 (86.6)	889 (81.6)	1359 (80.0)	824 (91.6)	1554 (89.1)	676 (89.9)
1 Symptom	550 (8.4)	884 (7.3)	91 (8.3)	141 (8.3)	44 (4.9)	122 (7.0)	31 (4.1)
2 Symptoms	261 (4.0)	480 (4.0)	71 (6.5)	123 (7.2)	21 (2.3)	39 (2.2)	31 (4.1)
3+ Symptoms	158 (2.4)	259 (2.1)	39 (3.6)	76 (4.5)	11 (1.2)	29 (1.7)	14 (1.9)

TABLE 4 Maternal symptoms potentially related to maternal COVID-19 infection during pregnancy among non-vaccinated women by COVID-19 antibody status at delivery and by site.

Symptoms during pregnancy	**Overall**		**Democratic Republic of the Congo**		**Zambia**		**Kenya**
Antibody results	+	−	+	−	+	−	+
Fever, *n* (%)	515 (7.8)	794 (6.5)	124 (11.4)	213 (12.5)	29 (3.2)	61 (3.5)	37 (4.9)
Cough, *n* (%)	337 (5.1)	585 (4.8)	53 (4.9)	82 (4.8)	40 (4.4)	89 (5.1)	15 (2.0)
Shortness of breath, *n* (%)	29 (0.4)	38 (0.3)	3 (0.3)	3 (0.2)	6 (0.7)	9 (0.5)	6 (0.8)
Chills, *n* (%)	136 (2.1)	253 (2.1)	72 (6.6)	122 (7.2)	13 (1.4)	24 (1.4)	31 (4.1)
Muscle pain, *n* (%)	135 (2.1)	247 (2.0)	41 (3.8)	74 (4.4)	7 (0.8)	22 (1.3)	15 (2.0)
New loss of taste or smell, *n* (%)	75 (1.1)	140 (1.2)	10 (0.9)	29 (1.7)	10 (1.1)	18 (1.0)	5 (0.7)
Vomiting or diarrhoea, *n* (%)	356 (5.4)	592 (4.9)	63 (5.8)	125 (7.4)	24 (2.7)	69 (4.0)	29 (3.9)
Sore throat, *n* (%)	52 (0.8)	97 (0.8)	1 (0.1)	4 (0.2)	2 (0.2)	7 (0.4)	0 (0.0)

TABLE 5 COVID-19 antibody positivity and symptoms during pregnancy among non-vaccinated women.

Putative symptoms of COVID-19 during pregnancy	**Delivery sample results**		**Single symptom models**[a]		**Multiple symptoms model**[b]	
	Positive	**Negative**	**RR (95% CI)**	***p*-Value**	**RR (95% CI)**	***p*-Value**
Fever, *n* (%)	515 (7.8)	794 (6.5)	1.10 (1.03–1.18)	0.008	1.13 (1.04, 1.23)	0.004
Cough, *n* (%)	337 (5.1)	585 (4.8)	1.03 (0.94–1.12)	0.534	0.98 (0.89, 1.08)	0.677
Shortness of breath, *n* (%)	29 (0.4)	38 (0.3)	1.27 (0.97–1.67)	0.082	1.25 (0.96, 1.64)	0.103
Chills, *n* (%)	136 (2.1)	253 (2.1)	0.97 (0.84–1.11)	0.628	0.91 (0.78, 1.05)	0.207
Muscle pain, *n* (%)	135 (2.1)	247 (2.0)	0.99 (0.86–1.14)	0.904	0.95 (0.82, 1.10)	0.468
New loss of taste or smell, *n* (%)	75 (1.1)	140 (1.2)	0.97 (0.81–1.17)	0.775	0.96 (0.79, 1.16)	0.669
Vomiting or diarrhoea, *n* (%)	356 (5.4)	592 (4.9)	1.01 (0.93–1.10)	0.748	1.00 (0.91, 1.09)	0.960
Sore throat, *n* (%)	52 (0.8)	97 (0.8)	1.12 (0.90–1.39)	0.327	1.08 (0.86, 1.35)	0.507

[a]Relative risks and 95% confidence intervals are obtained from generalised linear models with a binomial distribution and a log link adjusting for site and one symptom.
[b]Relative risks and 95% confidence intervals are obtained from a generalised linear model with a binomial distribution and a log link adjusting for site and all eight symptoms during pregnancy.

better understand these associations, we created a generalised linear model with a binomial distribution and a log link adjusting for site; this showed that among the symptoms, only fever was significantly associated with antibody status and this remained true when the model was further adjusted for all eight symptoms during pregnancy along with site.

4.2 | Interpretation

Most pregnant women infected with COVID-19 have either mild illness or are asymptomatic (and therefore might not get medical care or testing). Thus, antibody estimation allowed us to better understand the infection rate in the

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	Guatemala		India (Belagavi)		India (Nagpur)		Pakistan		Bangladesh	
–	+	–	+	–	+	–	+	–	+	–
1550 (67.3)	543 (23.6)	1762 (76.4)	655 (42.4)	889 (57.6)	810 (58.7)	569 (41.3)	776 (27.3)	2070 (72.7)	1058 (36.2)	1863 (63.8)
186 (12.0)	51 (9.4)	136 (7.7)	159 (24.3)	119 (13.4)	23 (2.8)	22 (3.9)	15 (1.9)	60 (2.9)	368 (34.8)	570 (30.6)
1550	543	1762	655	889	810	569	776	2070	1058	1863
1364 (88.0)	492 (90.6)	1626 (92.3)	496 (75.7)	770 (86.6)	787 (97.2)	547 (96.1)	761 (98.1)	2010 (97.1)	690 (65.2)	1293 (69.4)
62 (4.0)	32 (5.9)	94 (5.3)	115 (17.6)	95 (10.7)	16 (2.0)	17 (3.0)	7 (0.9)	34 (1.6)	214 (20.2)	319 (17.1)
82 (5.3)	11 (2.0)	30 (1.7)	21 (3.2)	15 (1.7)	6 (0.7)	4 (0.7)	5 (0.6)	15 (0.7)	95 (9.0)	172 (9.2)
42 (2.7)	8 (1.5)	12 (0.7)	23 (3.5)	9 (1.0)	1 (0.1)	1 (0.2)	3 (0.4)	11 (0.5)	59 (5.6)	79 (4.2)

	Guatemala		India (Belagavi)		India (Nagpur)		Pakistan		Bangladesh	
–	+	–	+	–	+	–	+	–	+	–
110 (7.1)	29 (5.4)	48 (2.7)	41 (6.3)	24 (2.7)	12 (1.5)	8 (1.4)	10 (1.3)	24 (1.2)	233 (22.0)	306 (16.4)
45 (2.9)	26 (4.8)	68 (3.9)	36 (5.5)	29 (3.3)	11 (1.4)	13 (2.3)	6 (0.8)	26 (1.3)	150 (14.2)	233 (12.5)
2 (0.1)	4 (0.7)	7 (0.4)	3 (0.5)	3 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)	6 (0.6)	12 (0.6)
77 (5.0)	6 (1.1)	8 (0.5)	13 (2.0)	8 (0.9)	0 (0.0)	1 (0.2)	0 (0.0)	11 (0.5)	1 (0.1)	2 (0.1)
50 (3.2)	5 (0.9)	6 (0.3)	18 (2.8)	6 (0.7)	0 (0.0)	1 (0.2)	7 (0.9)	21 (1.0)	42 (4.0)	67 (3.6)
17 (1.1)	4 (0.7)	8 (0.5)	9 (1.4)	2 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	37 (3.5)	64 (3.4)
66 (4.3)	1 (0.2)	10 (0.6)	124 (19.0)	84 (9.5)	6 (0.7)	5 (0.9)	3 (0.4)	17 (0.8)	106 (10.0)	216 (11.6)
4 (0.3)	11 (2.0)	42 (2.4)	7 (1.1)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	30 (2.8)	38 (2.0)

population.[16,17] In a population of non-vaccinated women, we assumed that the presence of COVID-19 antibodies were a marker of prior COVID-19 infection. Among these non-vaccinated women, we determined whether COVID-19 symptoms were related to COVID-19 antibody status. In this analysis, only fever was significantly related to antibody positivity, and that relation was weak. In addition, our analysis clearly demonstrated that the majority of the unvaccinated pregnant women with COVID-19 antibodies were asymptomatic. Equally important was the finding that the symptoms reported were generally similar in the women with and those without COVID-19 antibodies.

A large multi-site WHO study conducted across many states in India compared the pregnant women with COVID-19 disease with a matched control. Although this study used antigens rather than antibodies to define disease and was hospital-based, the results are in many ways comparable to our study. Most cases were asymptomatic and those who were symptomatic mostly had mild disease. Fever, as in our study, was the most common symptom.[18] There are many reports of COVID-19-related symptoms in women with active disease often defined by an acute illness, hospital admission and the presence of COVID-19 antigens. Importantly, these reports were generally not population-based but mostly included women with known disease.[19–24] The types and rates of symptoms in this type of study are clearly different from those found in our population-based study.

4.3 | Strengths and limitations

The presence of the ongoing, prospective, population-based MNH registry with a large sample size representing three regions of south Asia, sub-Saharan Africa and Central America, across seven LMIC countries with a standardised data collection method poses a unique strength to the study.[16] The results of antibody tests were not available at the time of symptom assessment, thus ruling out interviewer bias. Limitations include that we undertook analysis of presence of antibodies at delivery, and antibody estimation was not aligned with the actual presence of symptoms. One of the weaknesses of this study was that we did not know when the women who were antibody-positive had become antibody-positive or whether the women had become antibody-positive during

the pregnancy. We do, however, know on a population level that most of the antibody positivity increase in our sites occurred in the last 9 months of this study.

5 | CONCLUSIONS

Symptoms in non-vaccinated pregnant women who were COVID-19 antibody-positive were compared with those who were antibody-negative. Antibody-positive women had slightly more symptoms during their pregnancy and a small but significantly greater increase in fever. However, the differences were small. The relatively small differences in symptoms seen between antibody-positive and antibody-negative women make it unlikely that symptomology will be useful to discriminate between these women in population-based epidemiological studies. Therefore, it does not appear that one can use COVID-19-related symptoms to differentiate pregnant women who have a COVID-19 infection. The presence of one or more of these symptoms might lead a clinician to suspect a COVID-19 infection, especially during the pandemic, but it appears that using symptoms to diagnose a COVID-19 infection might lead to an inaccurate diagnosis.

AUTHOR CONTRIBUTIONS

RLG, SS, SkMB, EMM, PLH and NFK conceived the study with input from SSG, RJD, EC, AP, RH, MM, AT, WAP, FE, WAC, MB, SB and MK-T. JLM and EMM performed statistical analyses. AK, SSG, MSS, SS, SN, SkMB, RH, LF, MM, AL, AT, FE, MMw, EC, AP, PD and EMM oversaw the study implementation. AK wrote the first draft with inputs from RLG, EMM, SSG and MSS. All authors reviewed and approved the final article.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

All data presented in the manuscript will be available through the NICHD Data and Specimen Hub (N-DASH).

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