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OBSTETRICS

Boosting maternal and neonatal humoral immunity following SARS-CoV-2 infection using a single messenger RNA vaccine dose

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BACKGROUND: Post—COVID-19 vaccine boosting is a potent tool in the ongoing pandemic. Relevant data regarding this approach during pregnancy are lacking, which affects vaccination policy guidance, public acceptance, and vaccine uptake during pregnancy. We aimed to investigate the dynamics of anti—SARS-CoV-2 antibody levels following SARS-CoV-2 infection during pregnancy and to characterize the effect of a single postinfection vaccine booster dose on the anti—SARS-CoV-2 antibody levels in parturients in comparison with the levels in naïve vaccinated and convalescent, nonboosted parturients.

STUDY DESIGN: Serum samples prospectively collected from parturients and umbilical cords at delivery at our university-affiliated urban medical center in Jerusalem, Israel, from May to October 2021, were selected and analyzed in a case-control manner. Study groups comprised the following participants: a consecutive sample of parturients with a polymerase chain reaction—confirmed history of COVID-19 during any stage of pregnancy; and comparison groups selected according to time of exposure comprising (1) convalescent, nonboosted parturients with polymerase chain reaction—confirmed COVID-19; (2) convalescent parturients with polymerase chain reaction—confirmed COVID-19 who received a single booster dose of the BNT162b2 messenger RNA vaccine; and (3) infection-naïve, fully vaccinated parturients who received 2 doses of the BNT162b2 messenger RNA vaccine. Outcomes that were determined included maternal and umbilical cord blood anti—SARS-CoV-2 antibody levels detected at delivery, the reported side effects, and pregnancy outcomes.

RESULTS: A total of 228 parturients aged 18 to 45 years were included. Of those, samples from 64 were studied to characterize the titer dynamics following COVID-19 at all stages of pregnancy. The boosting effect was determined by comparing (1) convalescent (n=54), (2) boosted convalescent (n=60), and (3) naïve, fully vaccinated (n=114) parturients. Anti—SARS-CoV-2 antibody levels detected on delivery showed a gradual and significant decline over time from infection to delivery (r=0.4371; P=.0003). Of the gravidae infected during the first trimester, 34.6% (9/26) tested negative at delivery, compared with 9.1% (3/33) of those infected during the second trimester (P=.023). Significantly higher anti—SARS-CoV-2 antibody levels were observed among boosted convalescent than among nonboosted convalescent (17.6-fold; P<.001) and naïve vaccinated parturients (3.2-fold; P<.001). Similar patterns were observed in umbilical cord blood. Side effects in convalescent gravidae resembled those in previous reports of mild symptoms following COVID-19 vaccination during pregnancy.

CONCLUSION: Postinfection maternal humoral immunity wanes during pregnancy, leading to low or undetectable protective titers for a marked proportion of patients. A single boosting dose of the BNT162b2 messenger RNA vaccine induced a robust increase in protective titers for both the mother and newborn with moderate reported side effects.

Key words: anti SARS-CoV-2 antibody, boosting vaccine dose, case-control study, COVID-19, postinfection vaccine, pregnancy, single dose, vaccine during

Introduction

The COVID-19 pandemic remains an ongoing and evolving threat with novel variants emerging across the globe.[1] As the pandemic evolves, we learn about the decline in anti—SARS-CoV-2 antibody titers[2] and the emergence of new variants, which challenge our long lasting immunity following primary infection.[3] Importantly, recent data have indicated that a single booster dose of a messenger RNA (mRNA) vaccine significantly enhances resistance against variants of concern, including the B.1.617.2 (Delta)[4] and the B.1.1.529 (Omicron)[5] variants, via the hybrid immunity[4] phenomenon.

Pregnant patients are at increased risk for intensive care unit admission, mechanical ventilation, and death from COVID-19 when compared with properly matched, nonpregnant women.[6–15] Moreover, maternal COVID-19 morbidity and pregnancy-related complications dramatically affect fetal and neonatal health.[16]

Maternal anti—SARS-CoV-2 antibodies are an essential component of maternal antiviral immunity. In addition, maternal immunoglobulin G (IgG) antibodies cross the placental barrier and provide the first line of defense for neonatal humoral immunity. Boosting maternal IgG titers to enhance vertical protection is routinely implemented against pathogens like pertussis, for which antenatal maternal vaccination is used to prevent neonatal pertussis before infant vaccination.

During the course of 2020 to 2021, Israel instituted a nationwide campaign

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AJOG at a Glance

Why was this study conducted?

This study aimed to determine how anti−SARS-CoV-2 antibody levels change following infection during pregnancy and to characterize the effect of a single postinfection boosting dose.

Key findings

Anti−SARS-CoV-2 antibodies declined during pregnancy from infection to delivery. Following a diagnosis of COVID-19 in the first trimester, 34% of parturients presented with negative protective titers at delivery. Significantly higher anti−SARS-CoV-2 protective antibody levels were observed among boosted convalescent parturients when compared with the levels in nonboosted convalescent and naïve vaccinated parturients. Boosted convalescent parturients reported mild vaccine side effects.

What does this add to what is known?

Postinfection humoral immunity wanes during pregnancy to low or undetectable levels. A single boosting dose of the BNT162b2 messenger RNA vaccine induces a robust increase in protective titers for both mother and newborn.

to vaccinate the population with rapid uptake. After intense deliberations and in light of the increased morbidity and mortality observed among infected parturients and their offspring, it was determined that the risks associated with COVID-19 during pregnancy outweighed the potential risks associated with vaccination. The Israel Ministry of Health launched an unprecedented vaccination campaign and vaccinated pregnant patients with the Pfizer BNT162b2 mRNA vaccine.[17] In parallel, a single mRNA boosting dose was recommended for convalescent patients (at 3 months following infection) in light of the declining antibody titers among recovering COVID-19 patients and evidence that boosting improves cross-variant immunization.[4] Although pregnant women with a history of SARS-CoV-2 infection were included in this recommendation, data regarding the effectiveness and safety of the booster dose in this patient population were lacking. Consequently, primary care providers, obstetricians, and public health advisors were frequently asked about the effectiveness and safety of this policy, however, they encountered a gap in the relevant evidence available to substantiate their recommendations.

This unique population of convalescent pregnant patients who received a booster mRNA vaccine dose presents a rare opportunity to describe the effect of this immunization strategy during pregnancy. Such data are especially needed, because accumulating research supports the notion that pregnancy is a time of immune system modulation, affecting many aspects of the maternal immune response, including the humoral response.[18,19]

In this study we aimed to provide essential data regarding the dynamics of anti−SARS-CoV-2 antibody levels following SARS-CoV-2 infection during pregnancy (aim 1) and to characterize the maternal and neonatal impact of a single postinfection boosting dose of the Pfizer BNT162b2 mRNA vaccine (aim 2). In addition, we aimed to characterize the side-effect profile of the mRNA vaccine booster in pregnant patients with a history of SARS-CoV-2 infection (aim 3).

Materials and Methods

Study population

This study was based on an ongoing prospective biorepository cohort of parturients[17] recruited on admission to the delivery room from May 5, 2021 to October 25, 2021, at the Hadassah Mount Scopus Medical Center in Jerusalem, Israel. Eligibility criteria included an age of 18 to 45 years and a willingness to participate and provide informed consent. Pregnant women with active maternal COVID-19 at delivery were excluded from the study. The institutional review board of the Hadassah Medical Center approved the study (HMO-0389-20, HMO-0274-21).

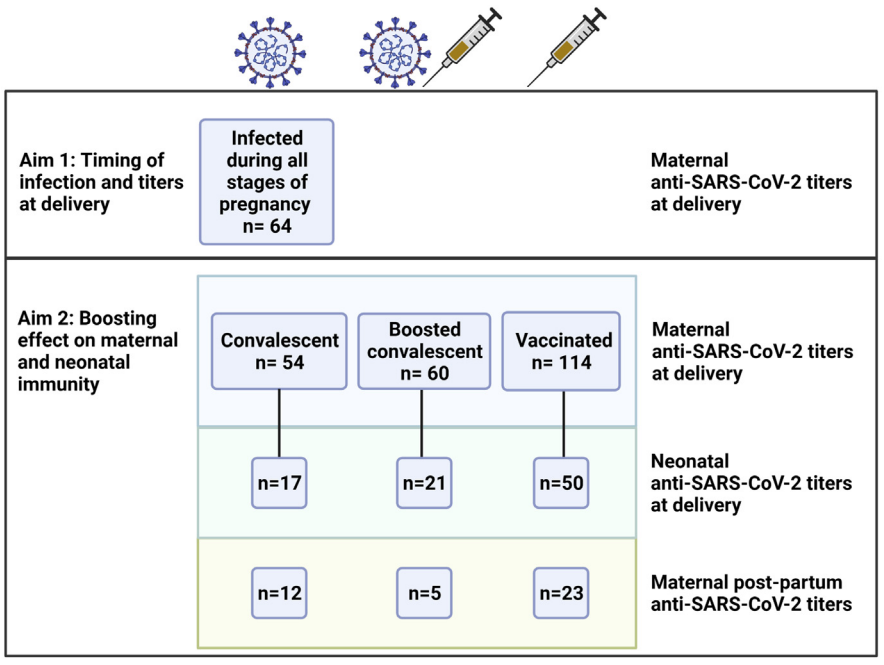
Because our first aim was to describe the impact of the time elapsed from infection to delivery on antibody levels in parturients with a history of COVID-19, we analyzed all available samples of unvaccinated patients infected at any time during pregnancy. SARS-CoV-2 infection was confirmed by a positive reverse transcriptase polymerase chain reaction test on a nasopharyngeal swab.

Subsequently (aim 2), parturients were assigned to 1 of 3 study groups, selected according to time of exposure, as follows:

1. Gravidae with a history of SARS-CoV-2 infection before or during pregnancy (from 29 weeks before pregnancy up to gestational week 22^{+0}) who did not receive a boosting vaccine dose were assigned to the convalescent group;
2. Gravidae with a history of SARS-CoV-2 infection before or during pregnancy (from 29 weeks before pregnancy up to gestational week 22^{+0}) who received a single boosting dose of the BNT162b2 mRNA vaccine during the index pregnancy (from gestational week 4^{+6} to week, 38^{+5}) were assigned to the boosted convalescent group;
3. Naïve, fully vaccinated controls with no history of SARS-CoV-2 infections who received 2 doses of the BNT162b2 mRNA vaccine and who received the second dose from gestational week 4^{+6} to week 38^{+5} were assigned to the vaccinated group.

For the participants, maternal and umbilical cord blood samples were drawn at the time of delivery and during the postpartum period for the mothers (maternal blood drawn, 6−13 weeks postpartum). Demographic, medical, and side-effect profile data were collected for all patients using the medical computerized chart and designated questionnaires (aim 3).

FIGURE 1
Patient selection flowchart (created with BioRender.com)



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A group of nongravid women of reproductive age was also recruited to characterize and compare the pattern of humoral response over time.

Sample and data collection and handling

Maternal and umbilical cord blood samples were collected immediately following delivery for patients who enrolled after they provided informed consent. Blood samples were centrifuged at 1000×g for 10 minutes at room temperature, and serum samples were aliquoted and stored at −80°C until analysis. Demographic and clinical data were collected at the time of enrollment.

Laboratory technique

Serum anti−SARS-CoV-2 spike receptor binding domain (RBD)−specific antibodies were assessed using the Architect SARS-CoV-2 IgG II Quant assay (Abbott Diagnostics, Chicago, IL).

For a subgroup of randomly selected mother-newborn dyads, neutralizing antibody titers against SARS-CoV-2 were determined using a wild-type SARS-CoV-2 microneutralization assay as previously described[20] with minor changes. Briefly, following serum heat inactivation, samples were serially diluted using 2-fold dilutions (starting from 1:10; diluted in Dulbecco's Modified Eagle's Medium in a total volume of 50 μL). Diluted samples were incubated for 1 hour at 37°C in a humidified atmosphere with 5% CO_2 with an equivalent volume of viral solution, including 100 median tissue culture infectious doses (TCID50) of SARS-CoV-2 isolate USA-WA1/2020 (cat. no. NR-52281; obtained from BEI Resources, Manassas, VA). The serum-virus mixtures (8 replicates for every serum dilution) were then added to a 96-well plate containing a semi-confluent VERO E6 cell monolayer (ATCC CRL-1586; maintained as described previously[21]). After incubation for 3 days at 37°C in a humidified atmosphere with 5% CO_2, the viral cytopathic effect was evaluated for each well. The median neutralization titer (NT50) was defined as the reciprocal of the highest serum dilution that protected 50% of culture wells from the cytopathic effect. Each assay included positive and negative serum controls, a cell control, and viral back-titration control.

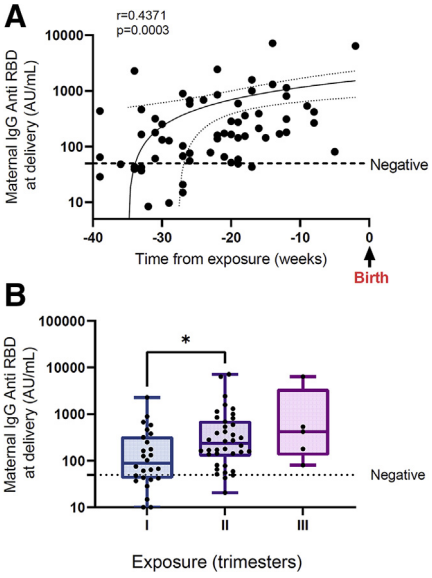
Statistical analysis

Statistical analyses were performed using IBM SPSS 27 for Windows (IBM Corp, Armonk, NY), and Prism 5.01 (GraphPad Software, San Diego, CA). Correlations between fetal and maternal antibodies were analyzed by linear regression tests. Comparisons of the antibody concentrations among groups, and continuous parameters (eg, clinical data), were analyzed using Kruskal-Wallis 1-way ANOVA tests followed by a Dunn all-pairwise comparisons test or, alternatively, using Wilcoxon rank sum tests (if only 2 groups were compared). Comparisons between maternal and fetal concentrations within each group were analyzed with Wilcoxon matched-pairs signed-rank test. A Pearson chi-square analysis was used to compare proportional data. All statistical tests were based on 2-tailed hypotheses. Differences were considered significant at a P value $<.05$.

Results

The study group comprised 228 parturients presenting for delivery at the Hadassah Medical Center as detailed in Figure 1. Figure 2 presents the longitudinal dynamics of anti−SARS-CoV-2 RBD antibody levels at delivery for the entire group of parturients infected during pregnancy plotted against the time since infection (aim 1). A clear and significant negative correlation can be seen between the time since infection and antibody levels (r=0.44; P=.0003) (Figure 2, A). Negative antibody results at the time of delivery were observed following infection during the first trimester for 34.6% (9/26) of parturients compared with 9.1% (3/33) of parturients who had an infection during the second trimester (P=.023). Figure 2, B displays the same relationship stratified by pregnancy trimesters in which infection occurred. Maternal anti−SARS-CoV-2 levels were significantly lower at delivery for women

FIGURE 2
Maternal anti−SARS-CoV-2 antibody titer decay across gestation



A, Maternal SARS-CoV-2 anti-RBD−specific immunoglobulin G (IgG) antibody concentrations at the time of delivery are plotted (y-axis) against the time of exposure (ie, positive RT-PCR, x-axis). Anti−SARS-CoV-2 RBD-specific IgG concentrations in maternal sera at delivery were positively correlated with the time from exposure (r=0.4371; P=.0003). **B,** Comparison of serologic data at delivery between women infected during the first (I), second (II), and third (III) trimesters. Differences among the groups were analyzed using a Kruskal-Wallis 1-way ANOVA test, followed by a Dunn multiple comparisons test. An *asterisk* indicates P<.05. For the box and whiskers plot, the *middle line* indicates the median, the *box* indicates the interquartile range, and the *whiskers* represent the minimum and maximum.

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infected during the first trimester than for those infected during the second trimester (P<.05).

The Table presents the demographic and clinical characteristics of the 3 study groups, and the median time from exposure (infection, boosting, or vaccination) to delivery and the median time from delivery to the second blood sampling, which occurred in the postpartum period. The clinical parameters did not differ among the groups nor did the neonatal outcomes. The distribution of exposures throughout gestation is further presented for all study groups using violin plots (Supplemental Figure A), and the time from infection to boosting interval (in weeks) in the convalescent boosted group is also presented (Supplemental Figure B).

Figure 3 presents the anti−SARS-CoV-2 antibody levels in the 3 study groups (aim 2). A single postinfection boosting dose of the mRNA vaccine elicited a robust humoral response, as shown by significantly higher antibody titers at delivery in the boosted convalescent group than in the nonboosted convalescent parturients (17.6-fold) and the naïve vaccinated parturients (3.2-fold). Similar patterns were observed among nongravid patients (Figure 3, gray box).

To evaluate transplacental vertical transmission of anti−SARS-CoV-2 antibodies, we analyzed the antibody levels and neutralizing activity in paired maternal and umbilical cord blood samples (88 maternal-umbilical cord blood dyads analyzed for antibody levels [Figure 4, A] and 12 dyads analyzed for neutralization activity [Figure 4, B]). Anti−SARS-CoV-2 antibody levels in the umbilical cord blood samples were found to be strongly correlated with and significantly higher than in the maternal blood samples in all 3 study groups (boosted convalescent: r=0.46; P=.0007; convalescent: r=0.93; P<.0001; naïve vaccinated: r=0.72; P<.0001). Both maternal and umbilical cord blood levels were significantly higher in the boosted convalescent and in the naïve vaccinated groups than in the convalescent group (Figure 4, A). Neutralizing SARS-CoV-2 antibody titers were further assessed in 12 representative maternal-umbilical cord blood dyads of convalescent and boosted convalescent dyads (Figure 4, B). Both maternal and umbilical cord blood neutralizing activity (as reflected by NT50 values) were significantly higher in the boosted convalescent group than in the convalescent group.

Figure 5 shows the antibody level dynamics during the postpartum period for all 3 study groups. Significant decay in the anti−SARS-CoV-2 antibody titers was evident in the naïve vaccinated group (P<.001). A similar trend of antibody waning was observed for the boosted convalescent group, although this did not reach statistical significance (P=.062), and no change was observed in the convalescent group (Figure 5, A). Six women in the convalescent group received a booster shot during the postpartum period at a median time of 5 weeks after delivery. This led to a robust surge in anti−SARS-CoV-2 antibody levels (Figure 5, B).

Figure 6 depicts the side-effect profile of the boosted convalescent group compared with the side-effect profile of the second shot in the naïve vaccinated group (aim 3). Although the side-effect profile patterns seemed to be similar to a large extent, boosted convalescent patients reported significantly lower rates of myalgia, injection site pain, and general malaise. Our study findings are summarized in Supplemental Videos 1 and 2.

Discussion

This study aimed to provide essential data regarding the dynamics of anti−SARS-CoV-2 antibody levels following SARS-CoV-2 infection during pregnancy and to characterize the effect of a single postinfection boosting dose with the Pfizer BNT162b2 mRNA vaccine. Our data show a gradual decline in the anti−SARS-CoV-2 antibody levels over time during pregnancy following infection, similar to what was described for the general population.[22−25] Boosting of convalescent pregnant women led to a robust upsurge in neutralizing antibody titers in both maternal and umbilical cord blood, detected at delivery, when compared with those in recovered nonboosted patients. In addition, antibody levels were monitored through the postpartum period for all study groups. Finally, within our small cohort, boosting of convalescent pregnant patients produced a mild side-effect profile, resembling the standard COVID-19 vaccination side-effect profile when vaccinated during pregnancy.

In their recent articles, Atyeo et al[18] and Bordt et al[26] highlighted the substantial differences in immune response to mRNA-based vaccines between

TABLE
Maternal and neonatal characteristics and outcomes of the 3 study groups

Characteristics	Boosted convalescent n=60	Convalescen n=54	Naïve, fully vaccinated n=114	*P* value
Obstetrical and demographics characteristics				
Maternal age at delivery (y)	27.0 (24.0–32.0)	28.0 (24.0–33.3)	29.5 (25.0–34.0)	.179
Body mass index (kg/m^2)	23.7 (21.5–27.6)	24.4 (21.5– 27.7)	24.5 (21.7–27.6)	.942
Parity	2 (0–3)	2 (1–4.3)	2 (1–3)	.097
Maternal smoking	2 (3.4%)	2 (3.7%)	3 (2.6%)	.917
Hypertensive disorders of pregnancy	0	0	5 (4.4%)	.078
Diabetes (pregestational and gestational)	3 (5.0%)	2 (3.7%)	1 (0.9%)	.232
Multifetal pregnancy	2 (3.3%)	2 (3.7%)	5 (4.4%)	.939
Preterm delivery	1 (1.7%)	3 (5.6%)	8 (7.0%)	.322
Gestational age at delivery (wk)	39.2 (38.3–40.0)	39.3 (38.4–40.3)	39.6 (39.0–40.4)	.040
Mode of delivery				
Vaginal delivery	52 (86.7%)	51 (94.4%)	100 (87.7%)	.370
Instrumental delivery	3 (5.0%)	1 (1.9%)	3 (2.6%)	
Cesarean delivery	5 (8.4%)	2 (3.8%)	11 (9.6%)	
Neonatal characteristics and outcomes				
Birthweight (g)	3225 (2794–3519)	3362 (3035–3655)	3334 (3030–3602)	.158
Neonatal sex (female)[a]	33 (55.0%)	20 (37.0%)	47 (41.2%)	.113
5-min Apgar score ≤7	1 (1.7%)	2 (3.7)	1 (0.9%)	.427
NICU admissions	0	1 (1.9%)	0	.198
Timing of events				
Gestational age at SARS-CoV-2 infection (wk)	10.7 (5.4–15.4)	12.3 (7.3–18.2)	—	<.001
Gestational age at vaccination or boosting (wk)	23.5 (17.0–32.1)	—	22.7 (19.3-27.3)	.534
Interval between infection and delivery (wk)	38.5 (28.3–50.5)	27.0 (21.8–34.0)	—	<.001
Interval between vaccination and delivery (wk)	15.0 (7.0–21.0)	—	19.0 (15.0–23.0)	<.001
Interval between delivery and post-partum sampling in weeks	11.0 (6.0–12.0)	7.0 (6.0–9.5)	8.0 (7.0–11.0)	.414
Interval between infection and vaccination in weeks	22.0 (17.0–29.5)			
Anti–SARS-CoV-2 titers				
Maternal titer at delivery	2608.0 (1223.0–8094.3)	148.3 (54.4–439.6)	797.7 (423.7–1622.9)	<.001
Cord titer at delivery	4891.5 (2210.6–7535.0)	171.7 (93.4–756.9)	2036.2 (946.7–4096.6)	<.001

Data are presented as number (percentage) or median (interquartile range). Continuous parameters were analyzed using Kruskal-Wallis 1-way ANOVA tests; Pearson chi-square analyses were used to compare proportional data.

[a] In cases of multiple gestation, baby A was selected for analysis.

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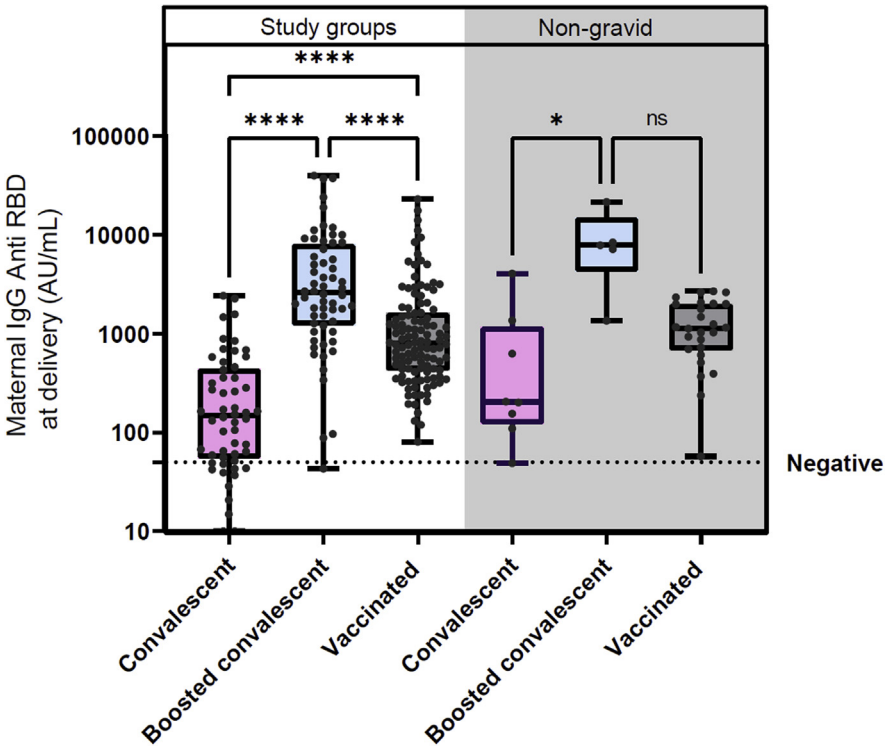
pregnant and nonpregnant women, urging the need to gather evidence based on pregnant patients.[18,19]

Anti–SARS-CoV-2 antibodies decline over time following infection,[22–25] a decline that has been linked to reduced protection against future symptomatic SARS-CoV-2 reinfection.[25,27,28] Boosting recovered patients with a single dose of an mRNA vaccine substantially enhances the immune response to SARS-CoV-2 variants.[29,30] This strategy induces a surge in protective titers equal to or higher than those achieved by 2 doses of the vaccine in people without previous infection.[31] Our study validates some of these findings during pregnancy. Recently, the American College of Obstetricians and Gynecologists adopted a boosting approach by recommending 2 vaccine shots in convalescent pregnant patients.[32] The significance and implementation of boosting in recovered pregnant women has stirred increasing

FIGURE 3
Maternal anti-SARS-CoV-2 antibody titers for study groups and non pregnant participants



Boosting convalescent patients with a single dose of the BNT162b2 messenger RNA vaccine, administered during pregnancy, elicited a robust surge in anti—SARS-CoV-2 antibody titers detected at delivery. SARS-CoV-2 anti-RBD—specific immunoglobulin (IgG) antibody titers for gravidae (*right panel*) and nongravid patients (*left panel*). The *pink box* represents convalescent participants, the *blue box* represents boosted convalescent participants, and the *gray box* represents naïve, fully vaccinated participants. The horizontal *dotted line* indicates a titer below 50 (negative result). Differences among the groups were analyzed using Kruskal-Wallis 1-way ANOVA tests, followed by a Dunn multiple comparisons test. *Quadruple asterisks* indicate a significance of $P<.0001$; *single asterisk* indicates a significance of $P<.05$. *ns*, nonsignificant.

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interest and discussion as the pandemic progresses. In Israel, where such a policy has already been implemented de facto for several months, healthcare providers and public health regulators continue to face questions regarding the necessity and impact of such a policy, emphasizing the urgency and demand for these data. Importantly, our results, revealing a vigorous surge in protective antibody levels in both the mother and the neonate in response to a single boosting dose, agree with a growing number of studies that suggest that a single dose of vaccine following infection may suffice.[30,31,33,34]

This study examined the SARS-CoV-2 antibody titer levels among pregnant and nonpregnant patients and found similar responses, which are comparable with previous reports of antibody levels following vaccination or disease in pregnant vs nonpregnant individuals.[35]

In addition, we did not examine the timing of vaccination during pregnancy to optimize neonatal seroprotection. However, Rottenstreich et al[36] analyzed sera samples from gravidae and their neonates at the time of delivery and compared those who were vaccinated early (27—31 weeks) with those who were vaccinated late (32—36 weeks) in their third trimester. The investigators showed that the earlier immunized group had enhanced transplacental antibody transfer and increased neonatal neutralizing antibody levels.[36]

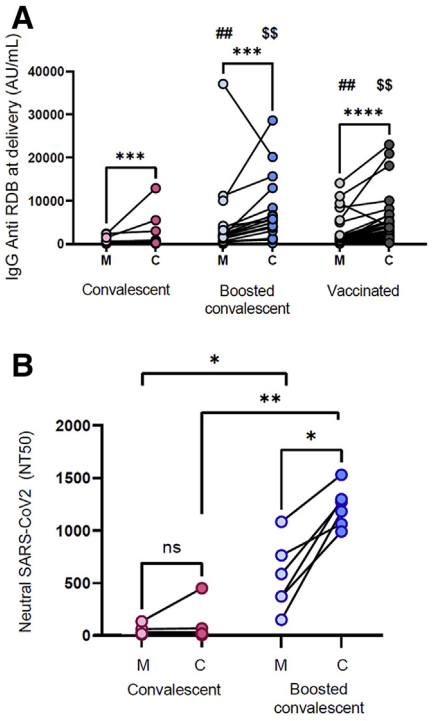
Professional obstetrics societies have widely promoted COVID-19 vaccination during pregnancy to minimize the risk for severe disease and its consequences.[37,38] Nevertheless, compliance among patients in numerous countries and societies are low[39,40] because general patient concerns regarding treatment during pregnancy persist. Our findings of a robust upsurge in maternal antibody levels in response to boosting after birth, along with previous reports of vertical transmission of humoral immunity during breastfeeding, may support an approach to augment maternal and neonatal immunity following delivery. Such policy may include boosting of parturients (who refused or were ineligible for treatment during pregnancy) shortly after delivery, during hospitalization, or as part of routine postpartum surveillance. This may significantly increase the uptake of vaccination in the peripartum period and augment immunity for parturients and offspring.

We also examined patient-reported side effects of post—COVID-19 vaccine boosting in pregnancy. We found that most reports did not differ from those of naïve vaccinees during pregnancy in our cohort. In fact, there were lower rates of myalgia, injection site pain, and general malaise when comparing mRNA boosting following infection with the second dose of the vaccine during pregnancy. Nevertheless, the number of participants is insufficient to draw conclusions regarding safety. Therefore, further studies are needed to substantiate the safety profile of such treatment during pregnancy——data that may aid the evidence-based decision-making process regarding the implementation of such a policy.

Strengths and limitations

This study provides the answers to a clinical question encountered by a wide range of physicians and healthcare providers. Its prospective nature, the use of a uniform and standard side-effect questionnaire that allows comparison with

FIGURE 4
Maternal protective anti–COVID-19 antibodies efficiently transfer to the fetus



A, The connected dot plots show SARS-CoV-2 anti-RBD–specific immunoglobulin G (IgG) antibody titers at delivery for maternal (M) and umbilical cord blood (C) pairs. *Pink dots* indicate the results for convalescent participants. *Blue dots* represent the results for boosted convalescent participants. *Gray dots* represent the results for naïve, fully vaccinated participants. Notably, 1 dyad of the boosted convalescent pairs showed a lower titer for the neonate than for the mother. This patient delivered 2 weeks following boosting. We speculate that the time elapsed from the boosting dose to delivery was insufficient for optimal vertical transmission. Significant differences between maternal and umbilical cord blood antibody levels within the same group was determined by a Wilcoxon matched-pairs signed-rank test. *Triple asterisks* indicate a significance of $P<.001$. *Quadruple asterisks* indicate a significance of $P<.0001$. Significant differences between maternal vs maternal (*hashtag* indicates $P<.0001$) and cord blood vs cord blood (*double dollars* indicate $P<.0001$) groups were found only when comparing titers with convalescent titers (Kruskal-Wallis 1-way ANOVA test, followed by a Dunn all-pairwise comparisons test). **B,** Maternal (M) and umbilical cord blood (C) sera neutralizing activity, reflected by NT50 values (provided in the Materials and Methods section), presented as maternal-cord pairs. Significant differences between the maternal and umbilical cord blood neutralizing activity within the same group was determined by a Wilcoxon matched-pairs signed-rank test and an unpaired *t* test for comparisons between groups. *Double asterisks* indicate a significance of $P<.01$. *Single asterisk* indicates a significance of $P<.05$.

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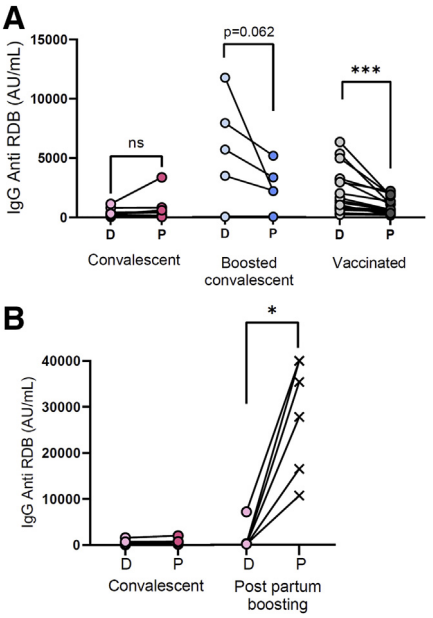
similar studies, comparison with non-gravid patients, and the use of well-established serologic assays, complemented by functional neutralization assays, all contribute to the robustness of our findings. In addition, although the samples were collected from only 1 center, our catchment area encompassed a diverse population. Our study is limited by the relatively small number of participants and the lack of long-term follow-up of the newborns. In addition, although studies support the notion that anti–SARS-CoV-2 antibody levels correlate with protection against symptomatic breakthrough reinfection,[25,27,28] immunologic memory is not restricted to antibodies alone. Memory B cells, memory CD4+ T cells, and memory CD8+ T cells may support protection[29,41] and were not evaluated in the present study. These important components of the immunologic response should be evaluated in further studies.

Conclusion

Our data demonstrate a significant decline in maternal antibody levels following SARS-CoV-2 infection during pregnancy. We present reassuring results regarding the potency of boosting convalescent gravidae with a single dose of an mRNA vaccine, showing that it provides a robust surge in neutralizing antibody titers with mild reported side effects. Given the observed decline in antibody levels before and during pregnancy, boosting strategies to enhance maternal and newborn anti–SARS-CoV-2 immunity may become the standard of care in the ongoing battle against novel SARS-CoV-2 variants. In this context, our work provides essential data to answer key questions that clinicians encounter daily and to support policy makers when deliberating the benefits of vaccine boosting in convalescent pregnant patients. ■

FIGURE 5
Anti–SARS-CoV-2 antibody titers following delivery and postpartum boosting



A, The connected *dot plots* show SARS-CoV-2 anti-RBD–specific immunoglobulin G (IgG) antibody titers at delivery and in the postpartum period for individual participants, presented as paired time points. *Pink dots* represent the results for convalescent participants, *blue dots* represent the results for boosted convalescent participants, and *gray dots* represent the results for naïve, fully vaccinated participants. Significance was determined using Wilcoxon signed-matched pairs test. *Triple asterisks* indicate significance of $P<.001$. **B,** The *dot plots* show SARS-CoV-2 anti-RBD–specific IgG antibody titers at delivery and in the postpartum period for individual participants, presented as paired time points. Convalescent participants (left) and convalescent participants who received a single postpartum boosting dose of the BNT162b2 messenger RNA vaccine (right).

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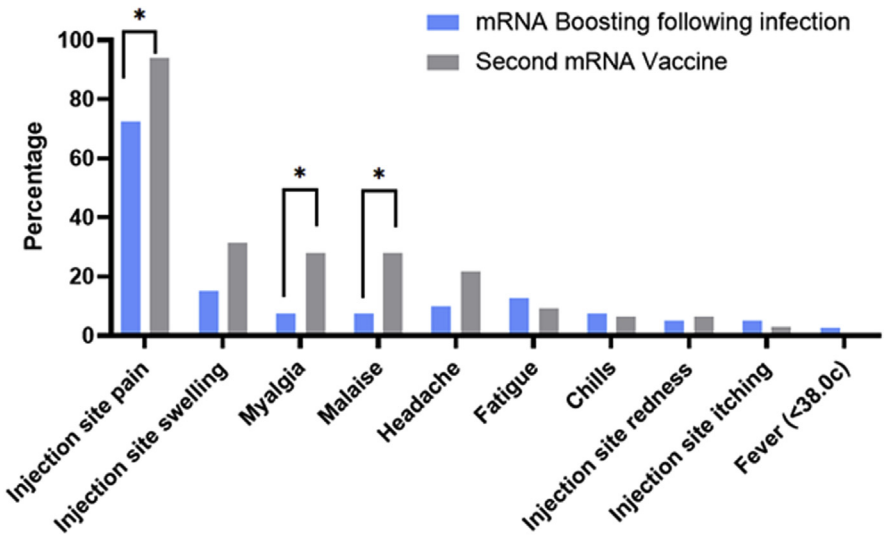
FIGURE 6
Comparison of side effects reported by participants following boosting and second mRNA vaccine



Most frequent local and systemic reactions reported after a single boosting dose of the BNT162b2 messenger RNA (mRNA) vaccine during pregnancy when compared with the second vaccine dose among naïve vaccinated parturients. Data are reported as the proportion of frequently reported side effects among convalescent parturients following vaccine boosting (*blue*) and following the second BNT162b2 mRNA vaccine (*gray*). Data were collected before or after labor using a detailed standard questionnaire. Differences between groups were analyzed using a Pearson chi-squared analysis. *Single asterisk* indicates significance of $P<.05$.

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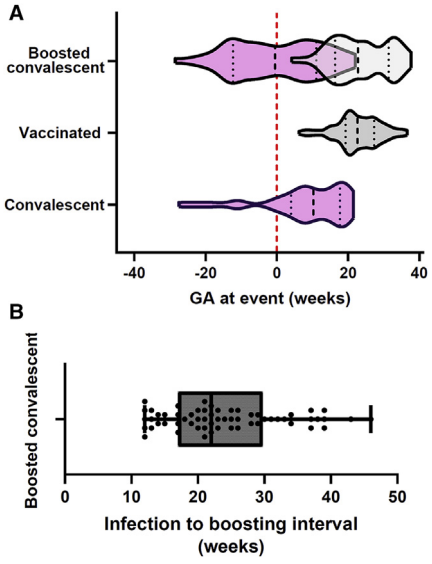
SUPPLEMENTAL FIGURE
Timing of study exposures



A, Gestational age (GA) at exposure for all study groups (*pink*: positive RT-PCR test; *gray*: booster dose or second vaccine dose). The *middle line* in each violin plot indicates the median. The *broken lines* indicate the 25th and 75th percentiles. The *red broken line* indicates the timing of last menses. **B,** *Box* and *whiskers plot* showing the duration of time from confirmed RT-PCR test to boosting vaccine dose among boosted convalescent participants. The *middle line* indicates the median, the *box* indicates the interquartile range, and the *whiskers* represent the minimum and maximum.

RT-PCR, reverse transcription polymerase chain reaction.

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