

ORIGINAL ARTICLE

Decreased severity of COVID-19 in vaccinated pregnant individuals during predominance of different SARS-CoV-2 variants

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Abstract

Problem: Since the start of the pandemic, Pregnant individuals have been disproportionately affected by the severe acute respiratory syndrome coronavirus 2. Vaccination has been shown to be protective against severe disease. However, data on effectiveness of vaccine in reducing disease severity are limited in pregnant individuals who later developed COVID-19.

Method of study: This is a single academic center retrospective cohort study of pregnant individuals who tested positive for COVID-19 from December 2020 through January 2022. The cohort was divided into two groups based on vaccination status. The primary outcome of our study was progression to severe or critical disease. A secondary analysis was performed based on the timeframes of predominance of different variants of SARS-CoV-2, to determine whether the effect of vaccination was different during these epochs.

Results: Our cohort included 472 patients among which 125 (26.5%) were vaccinated and 347 were unvaccinated. None of the patients in the vaccinated group who later developed COVID-19 progressed to severe or critical disease compared to 7.2% in the unvaccinated one ($p < .01$). Similarly, after adjusting for medical comorbidities, obesity, receipt of monoclonal antibodies, and trimester at diagnosis, vaccinated individuals who later developed COVID-19 were less likely to be admitted to the hospital (1.6% vs. 14.7%, aOR .14, 95% CI .22–.47) compared with unvaccinated ones.

Conclusion: Vaccination against SARS-CoV-2 in pregnant individuals who later develop a breakthrough infection, is associated with decreased progression to severe or critical COVID-19, and need for hospital and ICU admissions. Vaccination is specifically effective during the predominance of the more severe Delta variant.

KEYWORDS

COVID-19, pregnancy, SARS-CoV-2 variants, vaccination

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1 | INTRODUCTION

In March 2020, the World Health Organization (WHO) declared Coronavirus disease 2019 (COVID-19) as a pandemic worldwide.¹ Pregnant individuals have been affected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with increased rates of adverse outcomes.²⁻⁴ Disease severity in the pregnant population was worse during the predominance of the B.1.617.2 (Delta) variant compared with preceding variants such as B.1.1.7, B.1.351, P.1.^{5,6} Subsequently, data suggested that the highly contagious B.1.1.529 (Omicron) variant,⁷ was associated with milder disease outcomes compared to the preceding Delta variant.⁸

Pregnant individuals were excluded from the original SARS-CoV-2 vaccine trials.^{9,10} In January 2021, The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) issued a joint statement stressing that vaccines should not be withheld from pregnant individuals.¹¹ Vaccination was offered to pregnant patients and its use became more prominent as more reports regarding its safety became available.^{12,13} Since then, several studies have been published supporting the effectiveness and safety of the vaccine in pregnancy.¹⁴⁻¹⁷ However, these studies were limited as they included general population, did not account for the different variants, and did not address the effectiveness of the vaccine in reducing disease severity among those who later had a breakthrough infection.

The objective of our study was to determine whether vaccination against the SARS-CoV-2 virus was associated with reduced disease severity and improved outcomes among a cohort of pregnant individuals who developed COVID-19. We also compare the outcomes of vaccinated and unvaccinated patients during the different epochs of predominance of the major SARS-CoV-2 variants.

2 | MATERIALS AND METHODS

This is a single academic center retrospective cohort study that was conducted at The Ohio State University Wexner Medical center and approved by the University's Institutional Review Board. We included all pregnant individuals who tested positive for COVID-19 from December 2020 (when vaccination became available) through January 2022. At our institution, testing was performed for all individuals at the time of admission to the hospital for delivery, and for non-admitted ones who reported symptoms.

The primary exposure was SARS-CoV-2 vaccination status and the cohort was divided into two groups based on their status. The exposed group included fully vaccinated pregnant individuals whereas the unexposed group included unvaccinated individuals. Vaccinated individuals were defined as receiving at least 2 doses of BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) or one dose of Ad26.COV2.S (Janssen/Johnson & Johnson) vaccine. There were two individuals with incomplete vaccination receiving only one dose of mRNA-1273 (Moderna) vaccine and were excluded from the analysis.

Maternal and COVID-19 baseline characteristics were collected as well as clinical COVID-19 and perinatal outcomes. There was no difference in clinical care of patients at our institution based on vaccination status. The primary outcome of our study was progression to severe or critical disease as defined by the National Institutes of Health (NIH) criteria.¹⁸ Severe illness was defined as oxygen saturation less than 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) < 300 mm Hg, a respiratory rate > 30 breaths/min, or lung infiltrates > 50%. Meanwhile, critical illness was defined as respiratory failure, septic shock, and/or multiple organ dysfunction. Secondary outcomes included hospital admission due to COVID-19, intensive care unit (ICU) admission, need for oxygen supplementation, inpatient therapeutics (remdesivir and corticosteroids), maternal death secondary to COVID-19, monoclonal antibody infusion, and laboratories and imaging abnormalities. We also report pregnancy and perinatal outcomes.

At our institution, all pregnant individuals with mild or moderate COVID-19, and who presented within 10 days of symptom onset, were eligible to receive monoclonal antibodies. High-risk pregnant individuals who were admitted to the hospital with COVID-19, qualified for remdesivir. Those who required oxygen supplementation were also eligible for a course of corticosteroids. These interventions were based on the NIH treatment guidelines. The criteria for hospital admission did not change during timeframes of different variants predominance.

Summary statistics and bivariate analyses were performed for baseline variables and outcomes, as appropriate. Multivariable logistic regression was performed for COVID-19 outcomes adjusting for obesity (defined as body mass index (BMI) greater than 30 kg/m²) at time of COVID-19 diagnosis, receipt of monoclonal antibodies, trimester at diagnosis, and clinically relevant medical comorbidities (respiratory disease, diabetes, hypertension). Adjusted odds ratios with 95% confidence interval were calculated. Another multivariable logistic regression was performed for pregnancy and perinatal outcomes adjusting for obesity at time of COVID-19 diagnosis, nulliparity, trimester at diagnosis, advanced maternal age status, and clinically relevant medical comorbidities (respiratory disease, diabetes, hypertension). *p*-Value < .05 was used for statistical significance. No power calculations or correction for multiple comparisons were performed as this was an exploratory study with convenience sampling. All statistical analyses were performed using Stata version 15 (StataCorp, College Station, TX).

We also performed a secondary analysis based on the timeframes of predominance of different variants of the SARS-CoV-2, to determine whether the vaccination effects on outcomes were different during these periods. As individuals were not routinely sequenced for the different variants at our institution, three different timeframes of variants' predominance were identified based on CDC data for the state of Ohio.^{19,20} Timeframe 1 or the Pre-Delta variants (including B.1.1.7, B.1.351, P.1) spanned from December 2020-June 2021. Timeframe 2 or when the Delta (B.1.617.2) variant was predominant from the first week of July 2021 till December 16th, 2021. The third group is

TABLE 1 Maternal and COVID-19 characteristics

Maternal and COVID-19 characteristics (n)	Vaccinated (n = 125)	Unvaccinated (n = 347)	p-Value
Trimester at diagnosis ^a			<.01*
1 st	21 (17)	36 (10)	
2 nd	43 (34)	88 (26)	
3 rd	61 (49)	223 (64)	
Nulliparity ^a	36 (28.8)	75 (21.6)	.11
Advanced maternal age (≥35 years at delivery) ^a	21 (17)	42 (12)	.22
Medical comorbidities ^{a,b}	15 (12.0)	82 (23.6)	<.01*
BMI ≥ 30 at COVID-19 diagnosis (kg/m ²) ^a	55 (44.0)	212 (61.1)	<.01*
Diagnosis during prominent variant timeline ^a			<.01*
Pre-Delta	27 (21.6)	158 (45.5)	
Delta	39 (31.2)	122 (35.2)	
Omicron	59 (47.2)	67 (19.3)	
Monoclonal antibody infusion ^a	37 (29.6)	65 (18.7)	.01*

Abbreviations: BMI, body mass index; GA, gestational age.

^aData presented as n (%).

^bMedical co-morbidities = includes respiratory disease (asthma, COPD, or any other known underlying respiratory condition), chronic hypertension and/or pre-gestational diabetes.

*Significant at $p < .05$.

Timeframe 3 when the Omicron (B.1.1.529) variant was predominant from December 17th, 2021 through January 2022.

3 | RESULTS

A total of 474 pregnant individuals tested positive for SARS-CoV-2 infection at our institution during the study period. Two patients who were not fully vaccinated were excluded. Consequently, our cohort included 472 patients among which 125 (26.5%) were fully vaccinated and 347 (73.5%) were unvaccinated. The interval between completion of second dose of vaccine to diagnosis of COVID-19 was 4–24 weeks. The vaccinated group was more likely to be diagnosed with COVID-19 in the first and second trimester compared with the third trimester in the unvaccinated group ($p < .01$) (Table 1). The vaccinated individuals were less likely to have medical comorbidities (12.0% vs. 23.6%, $p < .01$) and obesity at time of COVID-19 diagnosis (44.0% vs. 61.1%, $p < .01$), while they were more likely to receive monoclonal antibody infusions (29.6% vs. 18.7%, $p < .01$) (Table 1).

None of the patients in the vaccinated group progressed to severe or critical disease compared to 7.2% in the unvaccinated group ($p < .01$). Similarly, the vaccinated individuals had a significantly lower odds to be admitted to the hospital (1.6% vs. 14.7%, aOR .14, 95% CI .22–.47) (Table 2), and to require corticosteroids (.8% vs. 10.4%, aOR .11,

95% CI .01–.52) or remdesivir (.8% vs. 12.4%, aOR .08, 95% CI .01–.37) when compared with the unvaccinated group (Table 2). None of the vaccinated patients were admitted to the ICU compared to 5.2% of the unvaccinated patients ($p < .01$). There were two maternal deaths in our cohort and both patients were unvaccinated (Table 2). Vaccinated patients were less likely to have laboratory abnormalities (8% vs. 31.7%, aOR .33, 95% CI .15–.65) and abnormal chest imaging (.8% vs. 12.4%, aOR .09, 95% CI .01–.42) (Table 2).

Pregnancy and perinatal outcomes were not significantly difference between the two groups (Table 3). None of the vaccinated individuals had a medically indicated preterm delivery due to worsening COVID-19 compared to 13 unvaccinated individuals who were delivered due to worsening disease (Table 3).

In this cohort, the overall rate of vaccination was 26.5%, and ranged from 14.6% in during timeframe 1 (Pre-Delta group), 24.2% during timeframe 2 (Delta group), to 46.8% during timeframe 3 (Omicron group) (Table 4). During timeframe 1, 3.7% of vaccinated patients were admitted to hospital secondary to COVID-19 compared with 14.4% of unvaccinated patients (aOR .33, 95% CI .02–1.78); and none of the vaccinated patients progressed to severe/critical disease compared with 4.4% of the unvaccinated ones ($p = .60$) (Table 4). During timeframe 2, no patients in the vaccinated group required admission to the hospital or progressed to severe/critical disease, compared to 18.9% ($p < .01$) and 11.5% ($p = .03$), respectively, in the unvaccinated group (Table 4). Likewise, during timeframe 3, 1.7% of vaccinated individuals were admitted to hospital compared with 7.5% of unvaccinated patients (aOR .14, 95% CI .01–1.05); none of the vaccinated patients progressed to severe/critical disease compared with 6% of the unvaccinated ones ($p = .12$) (Table 4).

4 | DISCUSSION

4.1 | Principal findings

In this retrospective cohort study that included 472 pregnant patients, the vaccination rate was 26.5%. None of the vaccinated individuals progressed to severe or critical COVID-19, and they were less likely to be admitted to the hospital or ICU. When evaluating timeframes of different variants predominance, vaccination was specially associated with improved clinical outcomes, during the predominance of the more severe Delta variant (Figure 1).

4.2 | Results in the context of what is known

Few studies have been published comparing clinical COVID-19 outcomes between vaccinated and unvaccinated individuals during pregnancy.¹⁴ After adjusting for baseline differences (obesity, medical comorbidities, trimester at diagnosis, and monoclonal antibody treatment) between our vaccinated and unvaccinated groups, a significant benefit was seen in vaccinated group with decreased COVID-19 severity and improved clinical outcomes. There was no difference

TABLE 2 COVID-19 characteristics, severity, and treatments

COVID-19 outcomes and treatments ^a	Vaccinated (n = 125)	Unvaccinated (n = 347)	OR (95% CI)	aOR (95% CI)	p-Value
Progression to severe/critical disease ^b	0	25 (7.2)	-	-	<.01*
Admission to hospital for COVID-19	2 (1.6)	51 (14.7)	.09 (.02-.35)	.14 (.22-.47)	-
Admission to ICU for COVID-19	0	18 (5.2)	-	-	<.01*
Symptomatic	93 (74.4)	227 (65.4)	1.54 (.97-2.47)	1.20 (.73-2.01)	
Oxygen supplementation					<.01*
Nasal cannula	1 (.8)	20 (5.8)			
HFNC	0	6 (1.7)			
Mechanical ventilation/ECMO	0	11 (2.7)			
Laboratory abnormalities ^c	10 (8)	79 (31.7)	.30 (.14-.57)	.33 (.15-.65)	-
Abnormal chest imaging ^d	1 (.8)	43 (12.4)	.06 (.01-.32)	.09 (.01-.42)	-
Receipt of corticosteroids for COVID-19	1 (.8)	36 (10.4)	.07 (.01-.40)	.11 (.01-.52)	-
Receipt of Remdesivir	1 (.8)	43 (12.4)	.05 (.01-.32)	.08 (.01-.37)	-
Maternal death from COVID-19	0	2 (.6)	-	-	.99

Note: aOR- adjusted odds ratio for obesity (Body mass index > 30), medical conditions (respiratory disease, chronic hypertension, and pre-gestational diabetes), receipt of monoclonal antibodies, and trimester at diagnosis.

Abbreviation: ICU: intensive care unit, HFNC: high flow nasal cannula, ECMO: extracorporeal membrane oxygenation.

^aData presented as n (%).

^bDefined using NIH criteria: Severe illness: SpO₂ < 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) < 300 mm Hg, a respiratory rate > 30 breaths/min, or lung infiltrates > 50%. Critical illness: respiratory failure, septic shock, and/or multiple organ dysfunction.

^cLaboratory abnormalities: Defined as platelet count less than 150 10³/UL, or prothrombin time greater than 14 s or partial prothrombin time greater than 35 s, or creatinine greater than 1 mg/dl, or Aspartate aminotransferase greater than 40 U/l or Alanine aminotransferase greater than 35 U/l.

^dChest imaging abnormalities defined by changes consistent with COVID-19 on chest X-ray or computed tomography.

*Significant at $p < .05$.

in the rate of symptoms' report between the two groups. However, symptoms reported by the vaccinated individuals are more likely to be mild or moderate as the vaccinated group had significantly less admissions to the hospital or the ICU compared to the unvaccinated group. Vaccinated patients were noted also to receive more monoclonal antibody treatments than their unvaccinated counterparts. This can be explained by the fact that patients who were willing to receive the vaccine would also be more willing to accept other forms of treatment compared to patients who declined vaccination. In addition, with vaccinated individuals having less severe symptoms and were less likely to be admitted, they were more often a candidate for monoclonal antibody infusions. Patients at our institution were offered same treatments including monoclonal antibody, regardless of vaccination status. In a previous study, we compared outcomes of patients who received monoclonal antibodies to those who were eligible but did not receive the treatment.²¹ It was noted that in vaccinated patients, monoclonal antibodies had no additional benefit in slowing the disease progression comparing to a significant benefit in unvaccinated patients. This further support the importance of vaccination as a preventative measure against severe COVID-19 disease and its sequelae.

With the progression of the pandemic, different variants were identified.^{19,20} Literature shows increased severity of the disease in pregnant individuals with COVID-19 during the Delta variant

predominance.^{6,22-24} We previously reported in a smaller cohort that included 99 patients with SARS-CoV-2 Delta variant, an increase in oxygen requirement and disease severity compared to preceding variants.⁵ In this study our cohort included 161 patients during timeframe 2 of Delta predominance and vaccination was found to be associated with decreased disease severity, similarly to previous reports.¹⁴

Unlike the increased illness severity seen with the Delta variant, the Omicron variant was associated with lower rates of COVID-19 severity.⁸ During Omicron predominance, vaccination was associated with less severe disease and decreased oxygen requirement in pregnancy.²⁵ While in our cohort none of the vaccinated patients progressed to severe disease or required oxygen during that era (timeframe 3), no statistical significance was detected. This difference between the studies' results could be explained by the relatively small sample sizes.

COVID-19 was shown to be associated with an increased risk of maternal mortality and morbidity from obstetrical complications.^{3,26} In terms of pregnancy and perinatal outcomes, our study did not show an increased risk in the vaccinated group compared to the unvaccinated one. This is in line with previous studies published in the literature showing no increased risk of preterm delivery, small for gestational age newborns, and cesarean section rate among other outcomes in vaccinated patients.^{27,28}

TABLE 3 Pregnancy and perinatal outcomes

Pregnancy and perinatal outcomes (n)	Vaccinated (n = 72)	Unvaccinated (n = 257)	OR (95% CI)	aOR (95% CI)	p-Value*
Gestational diabetes ^a	7 (9.7)	10 (3.9)	2.66 (1.02-7.06)	1.50 (.21-6.89)	-
Hypertensive diseases of pregnancy ^{a,b}	7 (9.7)	59 (23.0)	.43 (.18-.96)	.71 (.27-1.62)	-
Preterm premature rupture of membranes ^a	2 (2.8)	11(4.3)	.64 (.142-7.2)	.44 (.02-2.51)	-
Fetal growth restriction ^a	5 (6.9)	27 (10.5)	.64 (.26-1.71)	.59 (.16-1.63)	-
Cesarean delivery ^a	23 (31.9)	94 (36.6)	.81 (.46-1.39)	1.14 (.62-2.09)	-
Postpartum hemorrhage ^a	6 (8.3)	9 (3.5)	2.51 (.85-6.95)	3.23 (1.00-9.67)	-
Chorioamnionitis ^a	2 (2.7)	15 (5.8)	.46 (.11-1.75)	.54 (.08-2.07)	-
Medically indicated preterm delivery due to worsening COVID-19 ^a	0	11 (4.3)	-	-	.13
Preterm delivery < 37 weeks ^a	10 (13.9)	60 (23.3)	.53 (.26-1.07)	.55 (.25-1.04)	-
Birthweight (grams) ^c	3275 [3073-4490]	3235 [2803-3544]	-	-	.13
Small for gestational age ^a	6 (8.3)	33 (12.8)	.62 (.26-1.47)	.72 (.26-1.77)	-
NICU admission ^a	6 (8.3)	42(16.3)	.47 (.20-1.14)	.57 (.19-1.42)	-
Congenital fetal anomalies at birth ^a	1 (1.4)	6 (2.3)	.59 (.05-3.68)	.44 (.02-2.60)	-
Intrauterine fetal demise ^a	2 (2.8)	5 (1.9)	1.44 (.28-6.90)	1.41 (.07-11.50)	-

Note: aOR- adjusted odds ratio for obesity (Body mass index > 30), medical conditions (respiratory disease, chronic hypertension, and pre-gestational diabetes), advanced maternal age, nulliparity and trimester at diagnosis.

Abbreviation: NICU: Neonatal intensive care unit.

^aData presented as n (%).

^bHypertensive diseases of pregnancy include gestational hypertension, preeclampsia, HELLP syndrome, eclampsia.

^cData presented as median [interquartile range].

*Significant at $p < .05$.

TABLE 4 COVID-19 outcomes during different variants' predominance timeframes

	Vaccinated	Unvaccinated	OR (95% CI)	aOR (95% CI)	p-Value
Timeframe 1 or Pre-Delta group (n = 185)	27 (14.6)	158 (85.4)	-	-	-
Admission to hospital for COVID-19 ^a	1 (3.7)	23 (14.5)	.23 (.02-1.40)	.33 (.02-1.78)	
Admission to ICU for COVID-19 ^a	0	5 (3.1)	-	-	.99
Progression to severe/critical disease ^{a,b}	0	7 (4.4)	-	-	.60
Symptomatic ^a	18 (66.7)	98 (61.6)	1.25 (.55-3.03)	1.00 (.40-2.56)	
Timeframe 2 or Delta group (n = 161)	39 (24.2)	122 (75.8)	-	-	-
Admission to hospital for COVID-19 ^a	0	23 (18.9)	-	-	<.01*
Admission to ICU for COVID-19 ^a	0	10 (8.2)	-	-	.12
Progression to severe/critical disease ^{a,b}	0	14 (11.5)	-	-	.03*
Symptomatic ^a	34 (87.2)	92 (75.4)	1.78 (.69-4.90)	.96 (.30-3.41)	-
Timeframe 3 or Omicron group (n = 126)	59 (46.8)	67 (53.2)	-	-	-
Admission to hospital for COVID-19 ^a	1 (1.7)	5 (7.5)	.21 (.02-1.66)	.14 (.01-1.05)	-
Admission to ICU for COVID-19 ^a	0	3 (4.5)	-	-	.24
Progression to severe/critical disease ^{a,b}	0	4 (6.0)	-	-	.12
Symptomatic ^a	41 (69.5)	37 (55.2)	1.85 (.87-3.85)	1.60 (.67-3.91)	-

Note: aOR- adjusted odds ratio for obesity (Body mass index > 30), medical conditions (respiratory disease, chronic hypertension, and pre-gestational diabetes), receipt of monoclonal antibodies and trimester at diagnosis.

Abbreviation: ICU: intensive care unit.

^aData presented as n (%).

^bDefined using NIH criteria: Severe illness: SpO₂ < 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) < 300 mm Hg, a respiratory rate > 30 breaths/min, or lung infiltrates > 50%. Critical illness: respiratory failure, septic shock, and/or multiple organ dysfunction.

*Significant at $p < .05$.

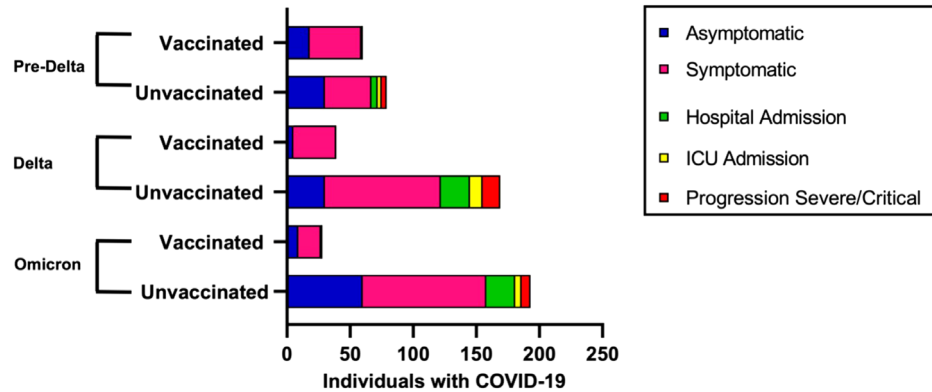


FIGURE 1 COVID-19 outcomes during different variants' predominance timeframes

4.3 | Clinical and research implications

Our study supports the previously published literature regarding COVID-19 vaccination in pregnancy and its importance in preventing severe illness with no major increase in adverse pregnancy or neonatal outcomes.^{14,29} Moreover, pregnant patients should be encouraged not to delay vaccination till the postpartum period as studies so far have not shown increased risk of pregnancy loss or any other adverse perinatal outcomes when vaccine is given during pregnancy.³⁰⁻³²

As stated earlier, with pregnant patients were excluded from the original vaccine trials, more prospective studies are needed in pregnancy to strengthen the existing evidence supporting the efficacy and safety of the vaccine in our population. Studies need to be inclusive of all the different population across the US and worldwide in order to allow for maximal generalizability of results and clinical application. Healthcare providers should counsel their pregnant patients regarding the existing evidence on vaccination and recommend it in a shared decision-making process.

4.4 | Strengths and limitations

One of the strengths of our study is the relatively large cohort of pregnant individuals positive for SARS-CoV-2 at a single academic center. We included all cases of COVID-19 at our center during the study period independent of time of diagnosis and pregnancy outcome. Our study also compared the effect of vaccination in timeframes of different variants' predominance. However, being retrospective, our study is limited by non-randomization of the two groups which was manifested by baseline differences in certain characteristics as noted above. In addition, our study was not powered to detect outcomes with low occurrence so conclusions from these outcomes cannot be generalized. We also did not have individual typing for each variant as it was not performed at our institution.

5 | CONCLUSIONS

Vaccination against SARS-CoV-2 in pregnant individuals is associated with improved clinical outcomes with decreased progression to severe

or critical COVID-19, hospital, and ICU admissions. Vaccination is specifically effective during the predominance of the more severe Delta variant. An increase in vaccination rate among pregnant individuals was seen with the progression of the pandemic. Healthcare providers should continue to promote awareness and encourage pregnant individuals to get vaccinated as more evidence supports their safety and effectiveness in pregnant individuals.

CONFLICTS OF INTEREST

The authors have no conflicts of interest or financial disclosures.

DATA AVAILABILITY STATEMENT

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

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