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Obstetric outcomes in women with rheumatic disease and COVID-19 in the context of vaccination status

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Abstract

Objective: To describe obstetric outcomes based on COVID-19 vaccination status, in women with rheumatic and musculoskeletal diseases (RMDs) who developed COVID-19 during pregnancy.

Methods: Data regarding pregnant women entered into the COVID-19 Global Rheumatology Alliance registry from 24 March 2020–25 February 2022 were analysed. Obstetric outcomes were stratified by number of COVID-19 vaccine doses received prior to COVID-19 infection in pregnancy. Descriptive differences between groups were tested using the chi-squared or Fisher's exact test.

Results: There were 73 pregnancies in 73 women with RMD and COVID-19. Overall, 24.7% (18) of pregnancies were ongoing, while of the 55 completed pregnancies, 90.9% (50) of pregnancies resulted in livebirths. At the time of COVID-19 diagnosis, 60.3% ($n=44$) of women were unvaccinated, 4.1% ($n=3$) had received one vaccine dose while 35.6% ($n=26$) had two or more doses. Although 83.6% ($n=61$) of women required no treatment for COVID-19, 20.5% ($n=15$) required hospital admission. COVID-19 resulted in delivery in 6.8% ($n=3$) of unvaccinated women and 3.8% ($n=1$) of fully vaccinated women. There was a greater number of preterm births (PTB) in unvaccinated women compared with fully vaccinated 29.5% ($n=13$) *vs* 18.2% ($n=2$).

Conclusions: In this descriptive study, unvaccinated pregnant women with RMD and COVID-19 had a greater number of PTB compared with those fully vaccinated against COVID-19. Additionally, the need for COVID-19 pharmacological treatment was uncommon in pregnant women with RMD regardless of vaccination status. These results support active promotion of COVID-19 vaccination in women with RMD who are pregnant or planning a pregnancy.

Video Abstract

A video abstract is available for this article and can be viewed at https://doi.org/10.1093/rheumatology/keac534.

Keywords: COVID-19, pregnancy, women's health, rheumatic disease, vaccination, patient outcomes

Rheumatology key messages

- Unvaccinated pregnant women with RMDs had a higher frequency of preterm birth than fully vaccinated.
- Hospitalization was common in pregnant women with RMDs regardless of COVID-19 vaccination status.
- COVID-19 vaccination should be encouraged in pregnant women with RMDs or those trying to conceive.

Introduction

Strategies to prevent or reduce adverse outcomes from coronavirus disease 2019 (COVID-19) have evolved rapidly over the past two years. This has been driven by improved understanding of disease transmission, greater effectiveness of preventative measures and rapid vaccine development including many large COVID-19 vaccine clinical trials [1, 2].

This has been an especially fraught time for pregnant women who were excluded from initial clinical trials of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines [3]. This resulted in little data to inform vaccination recommendations in pregnancy despite the risk of serious maternal and neonatal consequences [4]. Initial advisory panels recommended avoiding vaccination in the first trimester of gestation; however, this was revised following evaluation of additional safety data to encourage all pregnant women to be vaccinated at any stage of pregnancy [5, 6].

In pregnant women with rheumatic and musculoskeletal diseases (RMDs), there are additional considerations in managing pregnancy while trying to mitigate risk of COVID-19. Women with RMDs already face a higher risk of pregnancy complications, along with challenges of managing disease activity and the need to adjust to pregnancy safe therapy [7, 8]. Initial pregnancy outcomes of women with RMDs following COVID-19 from the COVID-19 Global Rheumatology Alliance (C19-GRA) were encouraging [9]. However, these results pre-dated data regarding vaccination safety in pregnancy [10] and timing of vaccination for RMD patients on immunosuppressive therapy [11]. Thus, this is the optimal time to re-evaluate a larger cohort of pregnant women with RMDs to fully understand the effect of COVID-19 vaccination on pregnancy.

In the general population, COVID-19 vaccination is associated with milder clinical symptoms, decreased hospitalizations and lower mortality in patients with subsequent COVID-19 [12]. Population studies have demonstrated this to also be true for vaccinated pregnant women [13]. Mild clinical courses of COVID-19 have been associated with lower risk of adverse obstetric outcomes in women of the general population compared with those with more severe COVID-19 [14], and it was extrapolated for vaccinated women with RMDs. However, there is limited data currently available on this issue.

The aim of this study was to describe obstetric outcomes in women with RMDs and COVID-19 in pregnancy in the context of vaccination status. This will provide valuable insight into pregnancy outcomes in vaccinated women following COVID-19.

Methods

The C19-GRA registry was established in March 2020 for healthcare professionals to record data on people with RMDs diagnosed with COVID-19. Details of the data recorded in this registry have been previously described [15]. We performed a cross-sectional analysis of women with COVID-19 during pregnancy. Data on pregnancy status was collected for all female patients entered into the original C19-GRA survey.

In addition to data previously collected by the C19-GRA from 24 March 2020–25 February 2022, this study collected several additional data points including COVID-19 vaccination status, details of current pregnancy and obstetric outcomes. Additional information on treatment of COVID-19 was gathered to reflect current treatments.

Supplemental data were collected via an electronic survey sent to healthcare professionals who submitted data on pregnant patients to the C19-GRA registry. Surveys were issued on 22 March 2022 and data collection concluded on 6 May 2022. Responses were received from 29 of 44 healthcare professionals (response rate = 65.9%) (Supplementary Fig. S1, available at *Rheumatology* online).

Frequency of pregnancy and neonatal outcomes were compared based on maternal vaccination status at the time of COVID-19. Specifically, outcomes were compared between unvaccinated or partially vaccinated women (0–1 dose) and those who were fully vaccinated (2 or more doses) [16]. Of note, none of the patients in this study received a single dose vaccine such as Johnson & Johnson.

Univariable comparisons were performed between partially/unvaccinated and fully vaccinated women using chi-squared test for independence or Fisher's exact test as appropriate. Data were analysed using IBM SPSS version 26 (alpha = 0.05).

The C19-GRA and EULAR registries have previously been deemed to be 'not human subjects research' under the US Federal Guidelines as assessed by the University of California at San Francisco and the UK Health Research Authority. For this reason, patient consent was not required. Full details of the ethics procedure for the C19-GRA have been previously outlined [15].

Results

Patient population

Data were collected from 73 women who were pregnant when they developed COVID-19, including data from 22 women previously published [9]. Mean age of participants was 32.3 years (S.D. 5.1, range 20–45). Systemic lupus erythematosus was the most frequent RMD diagnosis among pregnant women in the study (23.3%, $n = 17$), followed by rheumatoid arthritis (21.9%, $n = 16$) (Supplementary Table S1, available at *Rheumatology* online). RMD was in remission at time of COVID-19 diagnosis in 69.9% (51) of patients, with only 4.1% (3) reporting severe disease activity (Supplementary Table S2, available at *Rheumatology* online).

At the time of data extraction, 24.7% (18) of pregnancies were ongoing, while of the 55 completed pregnancies 90.9% (50) of pregnancies resulted in livebirths. Overall, 1.4% (1) of pregnancies resulted in miscarriage, and 4.1% (3) in stillbirths. One pregnancy resulted in termination for maternal health issues unrelated to COVID-19. Singleton pregnancies were reported in 95.9% (70), with one set of twins and two sets of triplets.

Vaccination status

Data on vaccination status at the time of COVID-19 was available for all participants; 60.3% (44) of participants were unvaccinated, 4.1% (3) were partially vaccinated, and 35.6% (26) were fully vaccinated at time of infection.

COVID-19 treatment

About one in five women (20.5%, $n = 15$) were hospitalized for COVID-19 with an average length of stay of 6.7 days (S.D. 3.4, range 1–14 days). Hospitalization was most common in unvaccinated women as reported in 22.7% (10), compared

Table 1. Pregnancy characteristics of women with RMDs following COVID-19 infection in pregnancy by number of doses of COVID-19 vaccination received

	Partially or unvaccinated		Fully vaccinated	
Number of COVID-19 vaccine doses:	**0**	**1**	**2**	**3**
Number of women	44	3	19	7
Number of pregnancies	44	3	19	7
Gravida[a]	2 (1.25, 3)	1 (1, 6)	3 (1, 4)	3 (1, 4)
Parity[a]	1.5 (1, 2)	0	1 (0, 3)	1 (0, 3)
Type of pregnancy				
Singleton	42	3	19	6
Twins	1	0	0	0
Triplets	1	0	0	1
Gestation (weeks)				
at COVID-19 diagnosis	24.6 (9.6)	16.7 (8.5)	18.7 (6.7)	22.3 (10)
at delivery	36.8 (4.2)	34.9 (4.7)	38.0 (0.9)	33.9 (9.5)
Preterm birth[b]	27.2% (12)	33.3% (1)	0	28.5% (2)
Fetal birth weight (grams)	3010 (600)	2400 (1100)	2920 (600)	3050 (500)
COVID-19 led to delivery	6.8% (3)	0	5.3% (1)	0
Hospitalisation for COVID-19	22.7% (10)	0	21.1% (4)	14.3% (1)
Duration (days)	8	N/A	4.5	6

Continuous variables reported as mean (S.D.), Categorical variables reported as % (*n*).
[a] Reported as median (25th, 75th centile).
[b] Defined as <37 weeks gestation at delivery.

Table 2. Pregnancy outcomes stratified by vaccination status in women with RMDs and COVID-19 results reported as % (*n*)

Vaccination status	Partially or unvaccinated[a]	Fully vaccinated[b]	*P*-value
Number of pregnancies	47	26	
Pregnancy outcome			
Pregnancy ongoing	6.4% (3)	57.7% (15)	
Completed pregnancies	93.6% (44)	42.3% (11)	
Livebirths[c]	93.2% (41)	81.8% (9)	0.26
Term birth[c]	63.6% (28)	72.7% (8)	0.57
Preterm birth[c]	29.5% (13)	18.2% (2)	0.45
Miscarriage	2.1% (1)	0	0.80
Termination	0	3.8% (1)	0.20
Stillbirth	4.2% (2)	3.8% (1)	0.50
Pregnancy-induced HTN	10.6% (5)	3.8% (1)	0.41
Pre-eclampsia	8.5% (4)	7.7% (2)	0.90
Gestational diabetes	10.6% (5)	3.8% (1)	0.41
PPROM	14.9% (7)	3.8% (1)	0.25
Neonatal complications[d]			
SGA[e]	12.2% (5)	22.2% (2)	0.43
LBW[f]	22% (9)	33.3% (3)	0.67
NICU admission required	12.2% (5)	0	0.27

[a] Defined as 0–1 dose of COVID 19 vaccine.
[b] Defined as 2 or more doses of COVID 19 vaccine.
[c] Of completed pregnancies.
[d] Reported in terms of livebirths.
[e] SGA defined as weight below the 10th percentile for gestation.
[f] LBW defined as birthweight <2500 g.
HTN: hypertension; LBW: low birthweight; NICU: neonatal intensive care unit; PPROM: premature rupture of membranes; SGA: small for gestational age.

with those who had received one dose of the vaccine (no hospitalizations), two doses (21.1%) or three doses (14.3%). ICU admission and intubation due to respiratory failure from COVID-19 was required in one patient who was unvaccinated at the time of COVID-19. No maternal deaths were reported. Need for pharmacological COVID-19 treatment was infrequent in this patient population, with 83.6% (61) patients requiring no treatment. This was consistent across all groups regardless of vaccination status.

Pregnancy outcomes

Pregnancy characteristics stratified by the number of COVID-19 vaccinations received is shown in Table 1.

COVID-19 was reported to have resulted in delivery in three (6.8%) unvaccinated patients and one patient (5.3%) who received two doses of the COVID-19 vaccine (Table 2).

Preterm birth (PTB) was the most common complication in the partially or unvaccinated group reported in 29.5% (13), higher than the 18.2% (2) reported in the fully vaccinated population ($P = 0.45$) in terms of completed pregnancies. A slightly higher prevalence of gestational diabetes, prolonged premature rupture of membranes (PPROM) and pregnancy-induced hypertension were also noted in the partially or unvaccinated group. However, these differences did not reach statistical significance.

Neonatal outcomes

Low birthweight (LBW) was the most frequent neonatal complication recorded in 24% (12/50) of pregnancies resulting in livebirths, followed by small for gestational age (SGA) in 14% (7/50). Number of livebirths in the vaccinated cohort was small, due to a large number of ongoing pregnancies at the time of data collection, making this a limited comparison. However, it was notable that neonatal intensive care admission occurred in 12.2% (5) of neonates from partially or unvaccinated mothers compared with none in vaccinated mothers despite similar rates of LBW (Table 2).

Discussion

This analysis describes pregnancy outcomes from a multinational cohort of women with RMDs from the C19-GRA registry. Data on 73 women each with a single pregnancy during the study period were included, providing insight into pregnancy outcomes in the setting of vaccination for women with RMDs.

The results of this study were reassuring with a similar prevalence of live births reported in all groups regardless of the number of vaccination status. However, hospitalization was relatively common in both unvaccinated and fully vaccinated groups (22.7% and 19.2%). Indication for hospitalization was not collected but as many of these women did not require treatment for COVID-19 it may be that admission was required for maternal and neonatal monitoring.

The mean gestation at delivery was <37 weeks, or preterm, in all groups with the exception of those who received two doses of the vaccine. This was consistent with the greater number of PTBs in the partially or unvaccinated group compared with fully vaccinated women (29.5% *vs* 18.2%). Of the three unvaccinated women in whom COVID-19 resulted in delivery, all three neonates were born preterm at 22-, 29- and 35-weeks' gestation with two neonates reported to have multiple complications. The delivery at 22 weeks was in a woman who required intubation in ICU for COVID-19 and resulted in a stillbirth. In comparison in the vaccinated group,

COVID-19 resulted in an early term delivery for one woman at 37 + 2 weeks with low birthweight at 2.3 kg as the only neonatal complication encountered.

PTB in the general population is known to be associated with an increased risk of multiple adverse neonatal outcomes including respiratory distress syndrome, feeding difficulties, worse neurodevelopmental outcomes and increased neonatal mortality [17]. Advances in obstetric monitoring and neonatal care are ongoing to improve outcomes in infants born preterm; however, minimizing risk of PTB remains a key goal of obstetric care [18].

The higher observed prevalence of PTB in those not fully vaccinated warrants further investigation. However, previous studies have demonstrated the association between COVID-19 and adverse pregnancy outcomes [19]. These results suggest vaccination of pregnant women with RMDs against COVID 19 may improve gestational age at delivery thus optimizing maternal and neonatal outcomes. Additionally, the low average gestational age of live births in this study supports the need for ongoing measures to limit risk of women with RMDs contracting COVID-19 during pregnancy.

Evaluation of neonatal outcomes in this study was limited as many pregnancies were ongoing in fully vaccinated women at time of data collection. In the partially or unvaccinated group, prevalence of LBW was high at 22% and 12.2% of neonates required admission to the NICU. This could reflect the higher prevalence of PTB in this cohort, or maternal COVID-19, both of which are associated with an increased risk of low birthweight in the general population [14].

The main limitation of this study was the small number of women and pregnancies included, precluding analysis beyond univariable comparison. Furthermore, these analyses were descriptive only and we were unable to adjust for confounding factors such as disease activity, comorbidities and medication usage. However, given the scant published data on COVID-19 in pregnant women with RMDs evaluating obstetric outcomes based on COVID-19 vaccination status, this study provides useful insights into obstetric outcomes in this setting.

This study had several strengths related to the patient population and reliability of the data. Firstly, the included women were multinational with a wide variety of ethnicities represented. The women also had a variety of RMDs including connective tissue diseases and inflammatory arthritis. Secondly, all data were submitted by clinicians caring for these patients during their pregnancy, with data extracted directly from medical records. This provided reliable data on patients' RMD and obstetric outcomes. Lastly, inclusion of data on vaccination status at the time of COVID-19 provided a unique perspective to comment on differences in obstetric outcomes of women with RMDs based on vaccination status. Although greater numbers of patients are needed to validate the findings suggested by this analysis, it provides a framework of design and focus for future studies.

Conclusion

This multinational analysis of obstetric outcomes in women with RMDs following COVID-19 using data from the C19-GRA registry is unique in the inclusion of vaccination data. Results of this study provide insights and evidence on the impact of vaccines on clinical course, need for delivery and prevalence of complications in pregnant women with RMDs. Unvaccinated or partially vaccinated women experienced a significantly higher frequency of PTB compared with those who were fully vaccinated. Regardless of vaccination status, the majority of patients did not require treatment for COVID-19, although hospitalisation was common. Ongoing data collection of obstetric outcomes in women with RMDs is needed to fully capture the impact of COVID-19 vaccination.

Supplementary data

Supplementary data are available at *Rheumatology* online.

Data availability statement

Request for access to data from the registry should be made to the Data Access and Sharing Committee of the COVID-19 Global Rheumatology Alliance. The data underlying this article are available on reasonable request to the corresponding author.

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