

## COVID-19 Infection and Disease Severity not associated with Increased Parity among Pregnant Women

Katharine A. Marsden BA<sup>1</sup>, Patrick P. Ten Eyck MS PhD<sup>2</sup>, Timothy N. Maxwell BS<sup>1</sup>, Claire N. Castaneda BSE<sup>1</sup>, Kimberly A. Kenne MD MCR<sup>3</sup>, Samantha R. Swartz BS<sup>4</sup>, Haley A. Steffen BA<sup>4</sup>, Anna E. Merrill PhD<sup>1</sup>, Matthew D. Krasowski MD PhD<sup>1</sup>, Abbey S. Merryman MD<sup>3</sup>, J. Brooks Jackson MD MBA<sup>1</sup> and Mary B. Rysavy MD<sup>3\*</sup>

<sup>1</sup>Department of Pathology, University of Iowa, Iowa City, IA.

<sup>2</sup>Institute for Clinical and Translational Science, University of Iowa, Iowa City, IA.

<sup>3</sup>Department of Obstetrics and Gynecology, University of Iowa, Iowa City, IA.

<sup>4</sup>University of Iowa Carver College of Medicine, Iowa City, IA.

### \*Correspondence:

Mary B. Rysavy, MD, Department of Obstetrics and Gynecology, University of Iowa, PFP 53215 200 Hawkins Dr, Iowa City, IA 52242.

Received: 02 May 2021; Accepted: 21 May 2021

**Citation:** Marsden KA, Ten Eyck PP, Maxwell TN, et al. COVID-19 Infection and Disease Severity not associated with Increased Parity among Pregnant Women. J Med - Clin Res & Rev. 2021; 5(5): 1-4.

### ABSTRACT

**Aim:** To compare prevalence and disease severity of Severe Acute Respiratory Syndrome Coronavirus 2 (COVID-19) among multiparous and nulliparous pregnant patients at a rural Midwest tertiary care hospital; parity used as a surrogate for having additional children, assessing if exposure to other coronaviruses is protective for COVID-19.

**Methods:** Retrospective cohort study included all patients who delivered at the University of Iowa between May 1, 2020 and September 22, 2020. Reverse transcriptase polymerase chain reaction and plasma antibody testing for COVID-19 were performed on women at the time of delivery. Demographics and outcome information were obtained from the electronic medical record. Adjusted odds ratio estimates for COVID-19 risk factors were obtained through the generalized linear modeling framework.

**Results:** In 1,001 delivering patients, 6.2% tested positive for COVID-19 by either viral or antibody tests. Comparing infection rates by parity strata revealed no significant distinctions, with 5.4% of nulliparous women and 6.7% of multiparous women positive by either test ( $p=0.41$ ). Odds of COVID-19 infection decreased by 6.2% for each year of maternal age ( $p=0.02$ ).

**Conclusion:** No significant associations were found between parity and prevalence or severity of COVID-19 infection in this population. Increasing maternal age and decreased COVID-19 frequency demonstrated a significant association.

### Keynotes

- 6.2% of the delivering population tested positive for Severe Acute Respiratory Syndrome Coronavirus 2 (COVID-19) by either reverse transcriptase polymerase chain reaction (RT-PCR) or antibody assay.
- There was no association between increasing parity and prevalence or severity of COVID-19 infection in this delivering pregnant population.

- A significant association was noted between increasing maternal age and decreased COVID-19 frequency.

### Keywords

COVID-19, SARS-CoV-2, Multiparity, Pediatric infection, Respiratory infections.

## Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (COVID-19) has been notable not only for its global spread and mortality, but also for its variable course. While adults are at higher risk for severe manifestations [1,2] children have overall experienced milder courses when infected and account for 1-3% of reported coronavirus cases [3-6]. This finding raised interest in possible cross-reactivity and preexisting immunity to COVID-19 from prior exposure to other seasonally spreading human coronaviruses (HCoVs) [1]. Cross reactivity has been supported by recent investigations by Shrock et al [7] and Ng et al [1] which found cross-reactivity to COVID-19 in COVID-19-uninfected people [1,7] and found it more often in younger cohorts [1]. However, overall results for cross-reactivity have been somewhat mixed [8-10]. Index cases of HCoVs are most frequently children under the age of eleven [4,11], and if more frequent exposure to HCoVs confers a degree of protection, it could be expected that other members of households with young children would also be exposed and might demonstrate some degree of immunity.

This study aimed to compare the prevalence and severity of COVID-19 infection among pregnant patients admitted for delivery at the University of Iowa Hospitals and Clinics (UIHC) from May 1 to September 22, 2020 with and without prior children in their household, using nulliparity and multiparity as markers for exposure to children in the household. The goal of our assessment was to estimate the association between having older children in a household and the rate and severity of COVID-19 infection in pregnant women.

## Materials and Methods

This retrospective cohort study comprised a population of 1001 unvaccinated pregnant patients, who all delivered consecutively at the University of Iowa Hospital between May 1, 2020 and September 22, 2020. As part of routine hospital admission care, COVID-19 reverse transcriptase polymerase chain reaction (RT-PCR) testing was performed on admission. Blood samples were also routinely collected, from which excess plasma was taken to determine the presence of COVID-19 antibodies. The institutional review board at the University of Iowa approved this study (IRB ID#: 202004278). The STROBE guidelines for observational studies were used for reporting of the study and results. The project was internally funded.

The residual EDTA plasma from patient blood samples taken at the time of delivery was tested for the presence of COVID-19 antibodies using the Elecsys® Anti-SARS-CoV-2 (Roche) and LIAISON® SARS-CoV-2 S1/S2 Immunoglobulin G (IgG) (DiaSorin) assays. Discrepancies between these two were resolved with the use of a third assay: the Abbott Architect® SARS-CoV-2 IgG assay or the EUROIMMUN Anti-SARS-CoV-2 ELISA IgG. The Roche assay targets the nucleocapsid (N) antigen, while the other assays target the spike (S) domain. Earlier studies have found that these assays show positivity 5-7 days after COVID RT-PCR positivity at the earliest. They are nearly 100% positive by day twenty-one [12,13].

We also estimated the association with asymptomatic, mildly symptomatic, and severely symptomatic manifestations of both nulliparous and multiparous women who had evidence of COVID-19 infection. The diagnosis of COVID-19 with mild symptoms was defined as having one or more of the following: upper respiratory congestion, headache, and GI symptoms. Moderate to severe cases of COVID-19 are indicated with the “severe” identifier and required electronic medical record (EMR) documentation of at least one of the following: Chest pain, cough, anosmia, ageusia, myalgia, dyspnea, or hypoxia. Nulliparity was defined as having no prior deliveries after 20 weeks gestation.

Demographic and clinical data for patients were obtained from the EMR. These data were double entered into a Research Electronic Capture (REDCap) database by two separate investigators. Discrepancies were identified by a third investigator and resolved.

Univariate and multivariate logistic regression modeling were used to test for a difference in COVID-19 infection between maternal parity (nulliparous and multiparous). We obtained unadjusted and adjusted estimates of outcome odds ratios, 95% confidence intervals, and p-values between parity strata. Maternal age and body mass index (BMI) were included as control measures in the multivariate models. Sub-setting on mothers who tested positive for COVID-19, Fisher’s exact test was used to compare symptom severity (asymptomatic, mild, moderate/severe) between parity strata and counts. All hypothesis testing was conducted at the  $\alpha = 0.05$  level.

## Results

Of the 1,001 pregnant patients who delivered at UIHC between May 1 and September 22, 2020, 59 (5.9%) tested positive by both Roche and DiaSorin assays for COVID-19 antibodies. Eight samples were discrepant between assays, which required resolution via the Abbott Architect® SARS-CoV-2 IgG assay (Table 1). Of these positive samples, 24 also tested positive by RT-PCR, and 3 tested positive via RT-PCR but were antibody negative. Therefore, 62 patients were found to have evidence of past or current COVID-19 infection, making up 6.2% of the study population. In total, 37.2% were nulliparous. Multiparous subjects made up 62.8% of the investigative group. Further results concerning COVID-19 infection and associated maternal and infant outcomes in this cohort were previously published [14].

Past or present COVID-19 infection was less common for nulliparous mothers (5.4%) compared to multiparous mothers (6.7%, Table 2), though this difference was not statistically significant (Unadjusted Odds Ratio (uOR): 0.794, 95% Confidence Interval (CI): 0.459 - 1.375,  $p = 0.41$ ). When adjusting for maternal age and body mass index, the difference between parity strata grows (Adjusted Odd Ratio (aOR): 0.649, 95% CI: 0.366 - 1.151), but still does not achieve statistical significance ( $p = 0.14$ ). Increasing BMI was associated with minimal decrease in infection risk (aOR: 0.991,  $p = 0.57$ ).

**Table 1:** Description of the study population.

Description of Study Population	
Characteristic	Population (n=1001)
Maternal age, Median (IQR)	30.0 years (26.0 - 33.0)
BMI, Median (IQR)	31.7 kg/m <sup>2</sup> (27.7 - 37.5)
Multiparous	62.8%
Nulliparous	37.2%
COVID-19 antibody positive <sup>a</sup>	5.9%
COVID-19 RT-PCR positive prior to or at admission	2.4%
COVID-19 RT-PCR positive and antibody negative	0.3%
Evidence of past/current COVID-19 infection	6.2%
Asymptomatic	31 (50.8%)
Mild symptoms	13 (21.3%)
Moderate to Severe symptoms	17 (27.9%)

<sup>a</sup>Antibody positive defined as a positive result on at least 2 of 3 assays including DiaSorin, Roche, or Abbott. There were 8 total discrepant samples. All but one were negative by the third assay.

**Table 2:** Severity of COVID-19 by parity.

	Asymptomatic	Mild	Severe	Total	P-value
Nulliparous	8	5	7	20	0.45
Multiparous	24	8	10	42	

**Table 3:** Severity of COVID-19 by increasing parity.

Parity	Asymptomatic	Mild Symptoms	Severe Symptoms	Total	P-value
0	8	5	7	20	0.82
1	11	5	6	22	
2	5	0	2	7	
3	5	3	1	9	
4	1	0	0	1	
5	0	0	1	1	
6	1	0	0	1	
7	1	0	0	1	
Total	32	13	17	62	

Increasing age did reach statistical significance, where each year of increase in age corresponded to a 6.2% decrease in risk of infection (aOR: 0.938,  $p = 0.02$ ). In this study population, the mean maternal age was 29.5 years (standard deviation = 5.3), with a range from 16 to 50 years.

No significant associations were observed between symptom severity and parity strata ( $p = 0.45$ , Table 2) or number of children ( $p = 0.82$ , Table 3). A very small proportion ( $n = 2$ , 3.3%) of COVID-19 positive patients considered in this cohort required admission to an Intensive Care Unit. When considering only antibody results (instead of both antibody and viral tests), a slightly increased protection from COVID-19 infection is seen for nulliparous mothers (uOR: 0.729, 95% CI: 0.413 - 1.289) but did not achieve statistical significance ( $p = 0.28$ ).

## Discussion

No significant associations were found between parity and the prevalence or severity of COVID-19 infection in this delivering

pregnant population. There was, however, a significant association between increasing age and COVID-19 status. The finding of decreased probability of COVID-19 infection with increasing age is surprising, as it appears to contradict observed trends showing increasing age as the strongest predictor of COVID-19 mortality [15-23]. However, there are several potential explanations for these findings.

This cohort still represents predominantly young women, with accordant overall good immunity. It cannot be ruled out that, having lived longer, these women could have been exposed to more HCoVs outside of the home, providing them some protection against COVID-19. Of the 1001 women who made up the initial cohort for this study, only 62 were COVID-19 positive by either viral PCR or plasma antibody. This relatively small proportion of COVID-19 infected women may have contributed to our findings. Because the investigatory population is pregnant women, it may reasonably be suspected that these women were taking additional precautions to avoid COVID-19 infection, which may have altered their susceptibility profiles.

Another potential limitation of this study is its location in a tertiary care academic medical center, with a higher attendant proportion of high-risk obstetrics compared to a community hospital setting. Finally, using parity as a measure of how many children reside in a household is a somewhat flawed measure, as it does not consider situations where nulliparous women may have children in the household (multigenerational households, adoptive children, stepchildren or other household types), nor does it account for situations in which multiparous women may not live with a child (stillbirth, neonatal loss, adoption). Additionally, this measure does not adequately determine if the children in the household attend school or daycare, which could represent an additional variable for increased COVID-19 exposure.

## Conclusion

Of the 1001 pregnant patients who delivered at the University of Iowa Hospitals and Clinics between May 1 and September 22, 2020, 62 were found to have evidence of a current or prior COVID-19 infection by RT-PCR or antibody positivity, making up 6.2% of the study population. There was no significant difference in the prevalence of COVID-19 or the COVID-19 disease severity for nulliparous compared to multiparous women.

## Acknowledgements

The study team would like to thank Laura Nicks, Farah El-Zein, and Ava Johnson for assistance in the blood bank with processing and storage of blood specimens.

## Complete list of abbreviations

BMI: Body mass index; COVID-19/SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; EMR: Electronic medical record; HCoVs: Seasonally spreading human coronaviruses; IgG: Immunoglobulin G; REDCap: Research electronic capture; RT-PCR: Reverse transcriptase polymerase chain reaction.

## Statements of conflict of interest and of funding

This study was funded internally and by a gift from Mark Gilbert and Karen Simmonds. There are no conflicts of interest to disclose. This study was supported in part by The University of Iowa Clinical and Translational Science Award granted with funds from the NIH (UL1TR002537).

## References

1. Ng KW, Faulkner N, Cornish GH, et al. Preexisting and de novo humoral immunity to SARS-CoV-2 in humans. *Science*. 2020; 370: 1339-1343.
2. Ludvigsson JF. Children are unlikely to be the main drivers of the COVID-19 pandemic - A systematic review. *Acta Paediatr*. 2020; 109: 1525-1530.
3. <https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/children/symptoms.html>
4. Davies NG, Klepac P, Liu Y, et al. Age-dependent effects in the transmission and control of COVID-19 epidemics. *Nature Medicine*. 2020; 26: 1205-1211.
5. Viner RM, Mytton OT, Bonell C, et al. Susceptibility to SARS-CoV-2 Infection Among Children and Adolescents Compared with Adults: A Systematic Review and Meta-analysis. *JAMA Pediatr*. 2020; 175: 143-156.
6. Li F, Li YY, Liu MJ, et al. Household transmission of SARS-CoV-2 and risk factors for susceptibility and infectivity in Wuhan a retrospective observational study. *The Lancet. Infectious Diseases*. 2021; 21: 617-628.
7. Shrock E, Fujimura E, Kula T, et al. Viral epitope profiling of COVID-19 patients reveals cross-reactivity and correlates of severity. *Science*. 2020; 18: 370.
8. Ju B, Zhang Q, Ge J, et al. Human neutralizing antibodies elicited by SARS-CoV-2 infection. *Nature*. 2020; 584: 115-119.
9. Tian X, Li C, Huang A, et al. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. *Emerging Microbes & Infections*. 2020; 9: 382-385.
10. Iyer AS, Jones FK, Nodoushani A, et al. Persistence and decay of human antibody responses to the receptor binding domain of SARS-CoV-2 spike protein in COVID-19 patients. *Science Immunology*. 2020; 5: eabe0367.
11. Monto AS, DeJonge PM, Callear AP, et al. Coronavirus Occurrence and Transmission Over 8 Years in the HIVE Cohort of Households in Michigan. *The Journal of Infectious Diseases*. 2020; 222: 9-16.
12. Merrill AE, Jackson JB, Ehlers A, et al. Head-to-Head Comparison of Two SARS-CoV-2 Serology Assays. *The Journal of Applied Laboratory Medicine*. 2020; 5: 1351-1357.
13. Miller TE, Garcia Beltran WF, Bard AZ, et al. Clinical sensitivity and interpretation of PCR and serological COVID-19 diagnostics for patients presenting to the hospital. *FASEB j*. 2020; 34: 13877-13884.
14. Steffen HA, Swartz SR, Jackson JB, et al. SARS-CoV-2 Infection during Pregnancy in a Rural Midwest All-delivery Cohort and Associated Maternal and Neonatal Outcomes. *Am J Perinatol*. 2021; 21: s-0041-1723938.
15. Ward H, Atchison C, Whitaker M, et al. Antibody prevalence for SARS-CoV-2 following the peak of the pandemic in England REACT2 study in 100,000 adults. *medRxiv*. 2020.
16. Pastor-Barriuso R, Pérez-Gómez B, Hernán MA, et al. SARS-CoV-2 infection fatality risk in a nationwide seroepidemiological study. *medRxiv*. 2020.
17. O'Driscoll M, Santos GRD, Wang L, et al. Age-specific mortality and immunity patterns of SARS-CoV-2 infection in 45 countries. *Med Rxiv*. 2020.
18. Perez-Saez J, Lauer SA, Kaiser L, et al. Serology-informed estimates of SARS-CoV-2 infection fatality risk in Geneva Switzerland. *The Lancet Infectious Diseases*. 2021; 21: E69-E70.
19. <https://www.cdc.gov/coronavirus/2019-ncov/COVID-data/investigations-discovery/hospitalization-death-by-age.html>
20. Metz TD, Clifton RG, Hughes BL, et al. Disease Severity and Perinatal Outcomes of Pregnant Patients with Coronavirus Disease 2019 (COVID-19). *Obstetrics & Gynecology*. 2021; 137: 571-580.
21. <https://www.who.int/news-room/q-a-detail/coronavirus-disease-COVID-19-pregnancy-and-childbirth>
22. Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy living systematic review and meta-analysis. *BMJ*. 2020; 370: m3320.
23. Zambrano LD. Update Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status United States, January 22–October 3, 2020. *MMWR Morb Mortal Wkly Rep*. 2020; 69: 1641-1647. <https://www.cdc.gov/mmwr/volumes/69/wr/mm6944e3.htm>