Increased COVID-19 Severity among Pregnant Patients Infected with SARS-CoV-2 Delta Variant, France

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DOI: https://doi.org/10.3201/eid2805.212080

We conducted a retrospective study of pregnant persons hospitalized for severe acute respiratory syndrome coronavirus 2 infection in France. Delta variant infection had a relative risk of 14.33 for intensive care unit admission and 9.56 for high supplemental oxygen support. The Delta variant might cause more severe illness during pregnancy.

The obstetric practice of Nord-Franche-Comté Hospital, France, has ≈3,600 deliveries per year (*1*). A recent study warned about the possibility of more severe coronavirus disease (COVID-19) among pregnant persons infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Delta variant (*2*). In France, the Delta variant became the predominant circulating SARS-CoV-2 variant in late June 2021 (*3*). We explored whether severe COVID-19 cases among pregnant persons increased in our facility when the Delta variant was predominant.

We conducted a retrospective study on all hospitalized pregnant women diagnosed with COVID-19 by reverse transcription PCR of nasopharyngeal swab samples during March 1, 2020–November 15, 2021. We defined severe COVID-19 as a case requiring intensive care unit (ICU) admission and critical COVID-19 as a case in the ICU that required high supplemental oxygen support, either high-flow nasal cannula, noninvasive ventilation, or mechanical ventilation.

We defined the predominant SARS-CoV-2 variants during 3 periods as variants detected in >50% of all sequences analyzed nationwide. National data from epidemiologic surveillance showed that wild-type was the predominant variant until March 1, 2021 (period 1); Alpha (20I/501Y.V1) during March 2–June 28, 2021 (*4*) (period 2); and Delta (21A/478K.V1) during June 29–November 15, 2021 (period 3). Beta (20H/501Y.V2) and Gamma (20J/501Y.V3) variants also were circulating in France but were not predominant.

To compare the frequency of severe and critical COVID-19 among the 3 periods, we calculated the ratio of women of reproductive age (defined as 15–42 years) hospitalized with COVID-19 during the same period. During March 1, 2020–November 15, 2021, a total of 77 women of reproductive age were hospitalized for COVID-19 in our facility, including 30 pregnant women (Figure). Among the 30 pregnant persons, 7 were transferred to the ICU (1 confirmed Alpha variant, 6 confirmed Delta variant

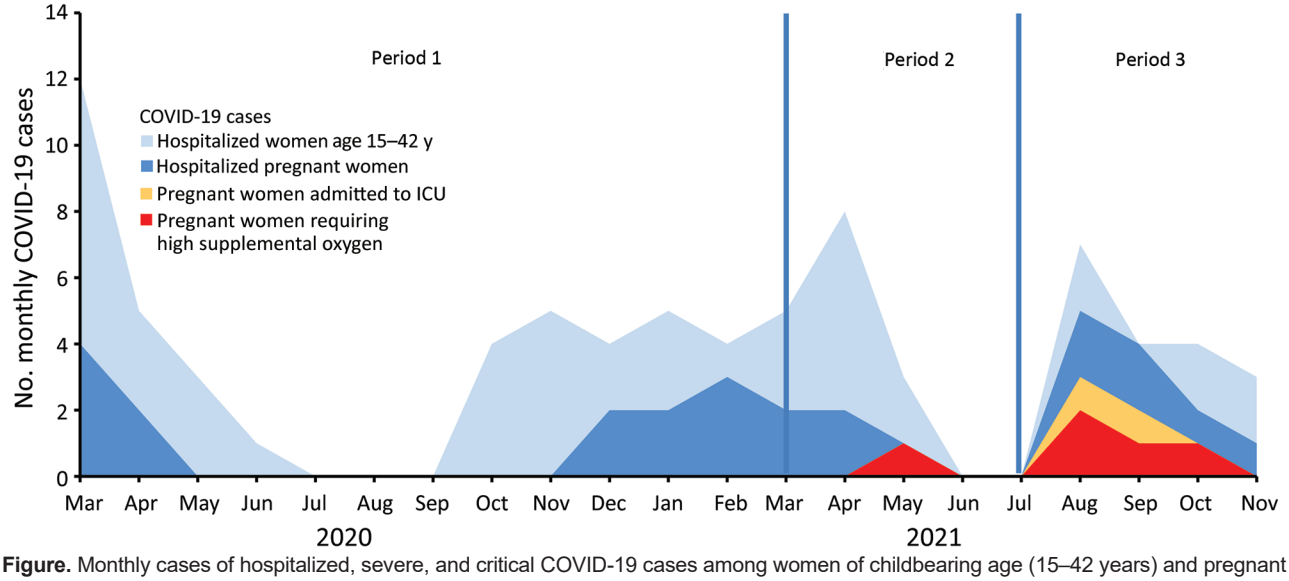

Figure. Monthly cases of hospitalized, severe, and critical COVID-19 cases among women of childbearing age (15–42 years) and pregnant women at Nord Franche-Comté Hospital, France, March 1, 2020–November 15, 2021. We assessed COVID-19 disease severity against circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants during 3 periods of interest based on predominance of circulating variants. During period 1, wild-type virus comprised >50% of all sequenced SARS-CoV-2 variants in France; during period 2, >50% were Alpha variant; and during period 3, >50% were Delta variant. COVID-19, coronavirus disease; ICU, intensive care unit.

cases), 5 of whom required high supplemental oxygen support (1 Alpha variant, 4 Delta variant cases). None of the 7 severe or critical COVID-19 patients were vaccinated.

For each period, we calculated the ratio between severe and critical COVID-19 among pregnant women and all women of reproductive age hospitalized for COVID-19. For period 1, the ratio was <2.33% (0 severe cases; thus, <1 among 43 cases); for period 2, 6.25% (1 severe case/16 cases); and for period 3, 33.33% (6 severe cases/18 cases). The ratio between pregnant women with critical COVID-19 and all women of reproductive age hospitalized for COVID-19 was <2.33% (0 critical cases; thus, <1 among 43 cases) for period 1; 6.25% (1 critical case/16 cases) for period 2; and 22.22% (4 critical cases/18 cases) for period 3.

Based on these ratios, compared with period 1, the relative risk for ICU admission was 2.69 (95% CI 0.18–40.46) for period 2 and 14.33 (95% CI 1.86–110.70) for period 3. The relative risk for high supplemental oxygen support was 2.69 (95% CI 0.18–40.46) for period 2 and 9.56 (95% CI 1.15–79.70) for period 3.

The risk ratios for severe and critical COVID-19 during the 3 periods rebut the hypothesis that the increasing number of SARS-CoV-2 infections in younger persons, combined with low acceptance for COVID-19 vaccination during pregnancy, sufficiently explain the increased risk for severe disease noticed with the Delta variant (*5*). SARS-CoV-2 lineage B.1.617 (Delta) probably is associated with increased COVID-19 severity among pregnant persons compared with previous variants (*2*,*6*). This consistent difference suggests a change in pathogenicity in pregnant persons and requires further investigation. A large retrospective cohort study comparing similar groups of pregnant women with COVID-19 during the pre-Delta period (n = 224) and the Delta period (n = 69) suggested an increase in critical illness and adverse perinatal outcomes associated with the Delta variant during pregnancy (*7*). Another study showed that pregnant patients infected with the Delta variant were more symptomatic and were diagnosed earlier than patients diagnosed before Delta was prevalent (*8*). Our results support the possibility of increased COVID-19 severity with Delta compared with previous SARS-CoV-2 variants.

Our study's first limitation is that standard care and hospitalization criteria changed between the 3 periods, which could have affected our results. We suspect thresholds for ICU admission were lower for pregnant persons during periods 2 and 3 than during period 1 because of a partial ICU bed saturation during the first COVID-19 wave (*9*). COVID-19 treatment progressively improved and standard care was more optimal during periods 2 and 3 than period 1(Appendix, https://wwwnc.cdc.gov/EID/article/28/5/21-2080-App1.pdf); thus, we should have expected fewer severe and critical COVID-19 patients in periods 2 and 3, but we observed the opposite. The main limitation of our study is the small sample size in a monocentric study, which prevents us from issuing any conclusions.

Despite the small number of cases, our findings on COVID-19 severity among pregnant persons infected with the Delta variant are consistent with those of other studies (*2*,*6*–*8*). A larger national cohort study, such as the one conducted by the UK Obstetric Surveillance System (N. Vousden et al., unpub. data, https://www.medrxiv.org/content/10.1101/2021.07.22.21261000v1), could confirm our findings. Nonetheless, our results show that SARS-CoV-2 prevention measures, especially COVID-19 vaccination, are needed during pregnancy.

Acknowledgments

We thank Azzedine Rahmani, Julien Huot, Elodie Bouvier, and Emmanuel Siess for their input into this work.

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Cross-Variant Neutralizing Serum Activity after SARS-CoV-2 Breakthrough Infections

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DOI: https://doi.org/10.3201/eid2805.220271

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To determine neutralizing activity against the severe acute respiratory syndrome coronavirus 2 ancestral strain and 4 variants of concern, we tested serum from 30 persons with breakthrough infection after 2-dose vaccination. Cross-variant neutralizing activity was comparable to that after 3-dose vaccination. Shorter intervals between vaccination and breakthrough infection correlated with lower neutralizing titers.

The B.1.1.529 (Omicron) variant of concern of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) carries a high number of nonsynonymous mutations in the spike glycoprotein, relative to that of the ancestral (wild-type) strain (Wu01). Those mutations result in a strong immune evasion phenotype, as demonstrated by severely reduced serum neutralization after vaccination or previous infection with ancestral variants in most persons (*1*–*3*), lower vaccine effectiveness, and increased rates of reinfection (N. Andrews et al., unpub. data, https://www.medrxiv.org/content/10.1101/2021.12.14.21267615v1). However, booster vaccinations with 1 dose of mRNA vaccine after priming with an initial 2 doses induce high levels of serum neutralizing activity against Omicron (*1*,*4*). Substantial efforts have therefore been made to speed up booster vaccination campaigns in light of the rapid spread of Omicron and the recent surge of infections worldwide. Breakthrough infections after 2-dose mRNA vaccination can result in a natural boost to humoral immunity against SARS-CoV-2 (*5*; L.J. Abu-Raddad et al., unpub. data, https://www.medrxiv.org/content/10.1101/2022.01.18.222694502v2), and emerging evidence suggests that breakthrough infections with non-Omicron SARS-CoV-2 variants also elicit cross-neutralizing serum activity against Omicron (*6*).

We determined serum neutralizing activity against the spike pseudotypes of SARS-CoV-2 Wu01 strain and 4 variants of concern (Alpha, Beta, Delta, Omicron [BA.1]) in 20 persons with non-Omicron (Alpha, Delta) SARS-CoV-2 infection after 2-dose mRNA vaccination with BNT162b2 (Comirnaty; Pfizer-BioNTech, https://www.comirnaty.com) or heterologous vaccination with ChAdOx1 (Vaxzevria; AstraZeneca, https://www.astrazeneca.com) and BNT162b2 (Appendix, https://wwwnc.cdc.gov/EID/article/28/5/22-0271-App1.pdf). We compared serum neutralization activity for this cohort with that of 2 age-matched cohorts, 1 consisting of 20 persons who received 2 or 3 doses of mRNA vaccine (*1*) and did not experience breakthrough infection and another cohort of 10 persons who experienced

Article DOI: https://doi.org/10.3201/eid2805.212080

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Appendix

Additional Conclusions

Pregnant persons with coronavirus disease (COVID-19) should receive low molecular weight heparin (LMWH) and proven therapies, such as corticosteroids and tocilizumab, on the basis of risk/benefit according to disease severity (*1*). Corticosteroids and tocilizumab were retained as proven therapies for COVID-19 in RECOVERY study results from June 2020 (*2*) and February 2021 (*3*). For these reasons, we think that during the first part of period 1 (up to March 1, 2021), standard care was less optimal than the other periods in our study (March 2–November 15, 2021).

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