

# Sickle cell disease, pregnancy, and COVID-19 in France: *plus ça change*

Lydia H. Pecker<sup>1,2</sup> and Jerome Federspiel<sup>3,4</sup>

<sup>1</sup>Division of Hematology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD; <sup>2</sup>Department of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Baltimore, MD; <sup>3</sup>Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Duke University School of Medicine, Durham, NC and <sup>4</sup>Department of Population Health Sciences, Duke University School of Medicine, Durham, NC, USA

**Correspondence:** L.H. Pecker  
lpecker1@jhmi.edu

**Received:** November 23, 2023.

**Accepted:** November 29, 2023.

**Early view:** December 7, 2023.

<https://doi.org/10.3324/haematol.2023.284457>

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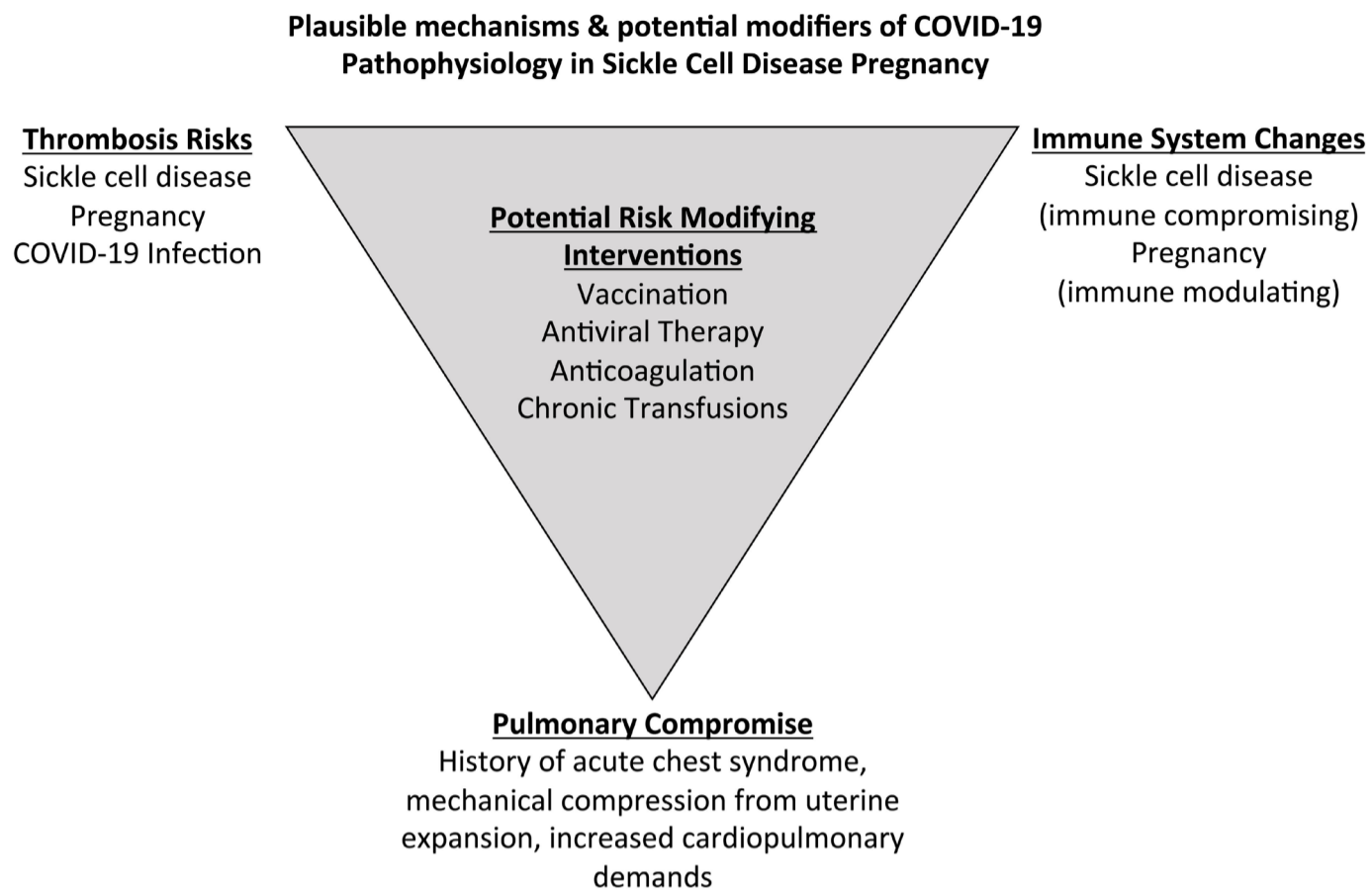
In this issue of *Haematologica*, Joseph and colleagues report outcomes of 28 pregnant individuals with sickle cell disease (SCD) diagnosed with coronavirus disease 2019 (COVID-19) whose data were collected in a French registry.<sup>1</sup> This is the first report addressing pregnancy outcomes in people with SCD and COVID-19 infection. This population of patients is exceedingly vulnerable as both pregnancy and COVID-19 infection are associated with increased morbidity and mortality in individuals with SCD.<sup>2,3</sup> Despite methodological limitations, the results suggest that the concurrence of SCD and COVID-19 produces synergistic hazards in pregnancy. The combination appears particularly perilous for the unvaccinated. In the study by Joseph *et al.*, 11 subjects with COVID-19 were hospitalized and only subjects who were unvaccinated required intensive care (5/11, 45%). The lone reported death in this series occurred in a 19-year-old subject with hemoglobin SC disease who was unvaccinated.

These attention-grabbing data underscoring the importance of COVID-19 vaccination for pregnant people with SCD nevertheless leave some unanswered questions. Was the subject who suffered a miscarriage vaccinated? What was the indication for COVID-19 testing among those treated as outpatients? How many cases occurred before the COVID vaccine or antiviral agents became available in France? Is the low rate of antiviral treatments explained by lack of availability or clear indication for use? Did the severe outcomes occur early in the pandemic before evidence-based management strategies and clear risks to pregnant people emerged?

Clearly, COVID-19 vaccination is essential for pregnant people with SCD. The overall COVID-19 vaccination rate in the cohort was low (30%). For the 16 subjects who had the alpha variant of COVID-19, the vaccine may have been unavailable at the time of infection. Whether there are racial disparities in vaccine uptake in France is unknown because federal law prohibits the collection of these data.

In the USA, most pregnant people with SCD are Black.<sup>2</sup> In the general population of pregnant people who are Black, COVID-19 vaccination rates are a disturbing 30%, consistent with the report from France.<sup>4</sup> However, the contemporary vaccination rate of individuals with SCD who receive care in specialized SCD centers in the USA may be as high as 70%.<sup>5</sup> Additional data are needed to appraise outcomes of COVID-19 vaccination uptake among pregnant people with SCD, to address intersectional disparities that may exist, and develop evidence-based strategies to encourage vaccination.

Respiratory symptoms are common in all pregnant people as pregnancy progresses and pulmonary complications are a significant feature of SCD, and SCD pregnancy.<sup>2</sup> It is thus unsurprising that compared to the non-hospitalized patients, hospitalized subjects with COVID-19 had more advanced gestational age (14 vs. 28 weeks;  $P=0.234$ ). In addition, compared to the non-hospitalized subjects, hospitalized subjects were more likely to have a history of acute chest syndrome (1 vs. 8;  $P=0.039$ ). Possibly, broader use of prophylactic chronic transfusions would have affected outcomes. British SCD Pregnancy Guidelines and American SCD Transfusion Guidelines indicate that a history of acute chest syndrome is an eligibility criterion for prophylactic transfusions in pregnancy.<sup>6,7</sup> In this study, overall, chronic prophylactic transfusion use was low ( $n=6$ ), with no difference in use of a chronic transfusion program between those who were and were not hospitalized (3 vs. 3). Only three of 11 hospitalized subjects received chronic transfusions in pregnancy; whether they were among the eight with a history of acute chest syndrome is unknown. There is evidence that chronic transfusions reduce pulmonary complications in pregnant women with SCD. A meta-analysis of observational studies of transfusion for pregnancy in women with SCD identified that chronic transfusions significantly reduced pulmonary complications during pregnancy (odds ratio=0.23; 95% confidence inter-



**Figure 1. COVID-19 may be particularly hazardous to people with sickle cell disease and pregnancy because of associated changes to the immune system, multiple thrombosis risks and compromised pulmonary function.** Given the risks, potential modifying interventions warrant consideration.

val: 0.11-0.50).<sup>8</sup> A recently published single-center, cohort study again demonstrated protective effects of transfusion on pulmonary complications in pregnancy in SCD.<sup>9</sup> Acute chest syndrome was among the SCD crises included as primary outcomes in the phase III hydroxyurea trial for adults with SCD and secondary outcomes in the phase III hydroxyurea trial for children with SCD. Reduction in acute chest syndrome was among the reasons for approval of hydroxyurea for both populations. Yet evidence of reduced SCD crises, including acute chest syndrome, in chronically transfused pregnant people with SCD has not yet widely shifted clinical practice even in resource-rich settings and despite alarming evidence of stagnant and poor pregnancy outcomes for this population.<sup>2</sup>

Multiple plausible mechanisms may explain why pregnant people with SCD are at increased risk of adverse outcomes in pregnancy (Figure 1). As any small study does, this cohort study raises more questions than answers. Until definitive answers arrive, multidisciplinary expertise for people with SCD who are pregnant may save lives and inform care.<sup>2</sup> Such care will integrate the unique strengths of maternal-fetal medicine and sickle cell experts. At a minimum, this care will include education and information about COVID-19 vaccination, individualized assessment of the need for antiviral medications in pregnant people with SCD who develop COVID-19 infection, tailor anticoagulation to address the triple thrombotic threat of SCD, pregnancy and COVID-19 infection, individualize

pain management, and appraise indications for chronic transfusion therapy. This will ultimately optimize both inpatient and outpatient care.

The COVID-19 pandemic presented novel risks for morbidity and mortality in pregnant people with SCD. Effective COVID-19 vaccines and therapies now exist and are complemented by evidence-based guidelines regarding their use.<sup>10</sup> Studying COVID-19 outcomes in SCD pregnancies is essential so that as new infectious threats emerge – as they also have with H1N1 influenza, severe acute respiratory syndrome, and Middle East respiratory syndrome – optimal management strategies can be rapidly defined and deployed. Underlying this is the enduring need for robust research to optimize the management of pregnancy in SCD. As the saying goes, *the more things change, the more they stay the same.*

#### **Disclosures**

*LHP is a consultant to Novo Nordisk and Global Blood Therapeutics (now Pfizer), co-founder of the Sickle Cell Reproductive Health Education Directive, and is on the Medical Advisory Committee of the Foundation for Women and Girls with Blood Disorders. JF has no conflicts of interest to disclose.*

#### **Contributions**

*LHP and JF interpreted the paper, wrote the manuscript and designed the figure together.*

**Funding**

*LHP is supported by the National Heart, Lung, and Blood Institutes of the National Institutes of Health under awards K23HL146841 and NIH/NHLBI U01 HL156620-01, the American Society of Hematology, Doris Duke Charitable Foundation Grant #2020147, and the Mellon Foundation. JF is supported*

*by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health under award K12HD103083. The content of this editorial is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health.*

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