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

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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 COVID-19 whose data was collected in a French registry. This is the first report addressing pregnancy outcomes in people with SCD and COVID-19 infection. This patient population is exceedingly vulnerable as both pregnancy and COVID-19 infection are associated with increased morbidity and mortality in individuals with SCD. Despite methodological limitations, the results suggest that cooccurring SCD and COVID-19 present synergistic hazards in pregnancy. The combination appears particularly perilous for the unvaccinated. In this study, there were 11 subjects hospitalized with COVID-19 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.

This attention-grabbing data underscoring the importance of COVID-19 vaccination for pregnant people with SCD nevertheless leaves 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 alpha variant, 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 this data. In the U.S.A., most pregnant people with SCD are Black. In the general population of
pregnant people who are Black, COVID-19 vaccine rates are a disturbing 30%, consistent with this report. 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%. Additional data is 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. 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, hospitalized subjects were more likely to have 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. 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 3 of 11 hospitalized subjects received chronic transfusions in pregnancy; whether they were among the 8 with a history of acute chest is unknown. There is evidence that chronic transfusions reduces pulmonary complications in SCD pregnancy. A meta-analysis of observational studies of transfusion for SCD pregnancy identified that chronic transfusions significantly reduce pulmonary complications in SCD pregnancy (OR, 0.23; 95% CI, 0.11-0.50). A recently published single-center cohort study again demonstrated protective effects of transfusion pulmonary complications in SCD pregnancy. Of course, acute chest
syndrome was among the SCD crises included as primary outcomes in the phase 3 hydroxyurea trial for adults with SCD and secondary outcomes in the phase 3 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 population².

Multiple plausible mechanisms may explain why pregnant people with SCD are at increased risk for adverse outcomes in pregnancy (Figure). As any small study must, this cohort study raises more questions than answers. Until definitive answers arrive, multi-disciplinary expertise for people with SCD who are pregnant may save lives and inform care². 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 thrombosis triple 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 a novel risk for morbidity and mortality for pregnant people with SCD. Effective COVID-19 vaccines and therapies now exist and are complemented by evidence-based guidelines regarding their use¹⁰. Studying COVID-19 outcomes in SCD pregnancy 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 these needs is the
enduring need for robust research to optimize the management of SCD pregnancy. As the saying goes, *the more things change, the more they stay the same.*
REFERENCES


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.
Plausible mechanisms & potential modifiers of COVID-19 Pathophysiology in Sickle Cell Disease Pregnancy

Thrombosis Risks
Sickle cell disease
Pregnancy
COVID-19 Infection

Immune System Changes
Sickle cell disease (immune compromising)
Pregnancy (immune modulating)

Potential Risk Modifying Interventions
- Vaccination
- Antiviral Therapy
- Anticoagulation
- Chronic Transfusions

Pulmonary Compromise
History of acute chest syndrome, mechanical compression from uterine expansion, increased cardiopulmonary demands