A study of 28 pregnant women with sickle cell disease and COVID-19: elevated maternal and fetal morbidity rates

Coronavirus disease 2019 (COVID-19) is known to be more severe during pregnancy and might increase the risk of adverse maternal and fetal outcomes. Several risk factors for severe COVID-19 have been identified, including older maternal age, being overweight/obese, non-white ethnicity, and comorbidities such as hypertension, diabetes, and lung diseases.[1,2] In the initial phase of the pandemic, COVID-19 was found to be less severe than expected in patients with homozygous sickle cell disease (SCD). In our recent, large study in France we found an elevated rate of severe complications among SCD patients with an SC genotype or those aged over 45 years.[3,4] Furthermore, maternal and fetal outcomes are worse (with more vaso-occlusive crises, preterm deliveries, preeclampsia, and thromboembolic events) in pregnant women with SCD than in the general population of pregnant women.[5] In contrast, little is known about the impact of COVID-19 on pregnant women with SCD. Here, we report on our clinical experience with 28 SCD pregnant women infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

On March 10, 2020, we invited all physicians at French SCD reference centers to prospectively register all SCD patients (including pregnant women) with COVID-19 (as confirmed by reverse transcriptase polymerase chain reaction testing of nasal swabs). The present analysis of de-identified patients' data was approved by a local institutional review board. In line with French legislation on retrospective studies of routine clinical practice, participants were not required to give their written, informed consent. However, all participants were given information about the study's objectives and procedures by telephone or by e-mail.

We used the Mann-Whitney test to analyze quantitative variables (expressed as the median [range]) and the Fisher exact test to analyze categorical variables. The statistical analyses were performed using GraphPad Prism software (version 9, GraphPad Software, La Jolla, CA, USA).

Twenty-eight pregnant women (median age [range]: 26.9 years [19.0-43.0]) were included by ten centers between January 1, 2020, and February 25, 2022 (Table 1). The COVID-19 occurred during predominance of the alpha variant in 16 cases, during predominance of the delta variant in one, and during the omicron peak in 11 (P=0.2847). There were 18 (64%) women with SS genotypes, seven with (25%) SC genotypes, two (7%) with Sβ^+ genotypes, and one (4%) with a Sβ^0 genotype. At the time of the diagnosis of COVID-19, 16 patients were admitted to hospital and 12 were not. The median age was similar in the inpatients (28.2 years [19.0-39.1]) and outpatients (26.9 years [19.0-43.0]). There were no intergroup differences in body mass index, prevalence of hypertension, or of diabetes mellitus. Of the 16 inpatients, ten had an SS genotype, five had an SC genotype, and one had an Sβ^0 genotype. Overall, there was no difference in the likelihood of hospital admission between the SS/Sβ^0 (57.9%) and SC (71.4%) SC/Sβ^+ subgroups (P=0.2811). A history of acute chest syndrome was more frequent among the inpatients than among the outpatients (8 *vs*. 1; P=0.039). There was no difference between inpatients and outpatients with regard to hemoglobin concentration, hydroxycarbamide prescription before pregnancy, prescription of a transfusion program, transfusion in the 60 days before the infection, and COVID-19 vaccination status (Table 1).

The duration of pregnancy at the time of the COVID-19 diagnosis was significantly longer among the inpatients, being a median of 28 weeks of gestation (WG) [5-37] in these patients compared to 14 WG [2-30] among the outpatients (P=0.034). The signs and symptoms of COVID-19 were quite similar to those described in the general population and did not differ when comparing the two groups (*data not shown*). Three patients experienced acute chest syndrome during their time in hospital, and two of eight patients who had undergone computed tomography presented the typical tomographic signs of COVID-19. Eight inpatients (50%) required a transfusion (n=5) or a manual exchange (n=3). Three inpatients received specific treatment for severe COVID-19 (a steroid [n=2] or tocilizumab [n=1).

The admissions were prompted by vaso-occlusive events (n=7; vaso-occlusive crises and/or acute chest syndrome) or induced deliveries (n=3) with a positive polymerase chain reaction test on admission and no specific symptoms of COVID-19. In addition, five patients were hospitalized for symptomatic COVID-19 without vaso-occlusive events on admission. Data were not available for one patient.

Five of the 16 inpatients (31%) were admitted to an intensive care unit (ICU); none of these five patients had been vaccinated. The median length of stay in the ICU was 8 days [3-30], and the median time interval between disease onset and admission to the ICU was 1 day [1-14] (Table 1). Three of these five patients had an SS genotype, and two had an SC genotype. Two patients (1 HbSS and 1 HbSC) required mechanical ventilation, and one of the latter required extracorporeal membrane oxygenation; both recovered without sequelae. One 19-year-old woman with an SC genotype died in a context of acute respiratory distress syndrome (initial acute chest syndrome, complicated by ventilator-acquired pneumonia), bone marrow necrosis, and multiorgan failure around 20 days after admission for a vaso-occlusive crisis related to the SARS-COV-2 infection.

Data on pregnancy outcomes were available for 23 of the 28 patients. We noted one miscarriage at 7 WG, 12 preterm births (1 extremely preterm, 3 very preterm, 3 moderate preterm,

Table 1. Characteristics of the study participants.

	Inpatients	Outpatients	*P*
Patients, N (%)	16 (100)	12 (100)	-
Genotype, N (%) SS/S-β^0 SC/S-β^+	 11 (68.8) 5 (31.2)	 8 (66.7) 4 (33.3)	 1.000
Age in years, median (range)	28.2 (19.0-39.1)	26.4 (20.0-43.0)	0.4166
BMI, kg/m², median (range)	25 (18-34)	21 (16-31)	0.1488
History ACS, N (%) ACS, total during life, median (range) Hypertension, N (%) Diabetes, N (%) Hydroxycarbamide, N (%) Transfusion program, N (%) Previous COVID-19, N (%) Vaccinated patient, N (%)	 8 (50) 0.5 (0-4.0) 2 (12.5) 1 (6.3) 5 (31.3) 3 (18.8) 1 (6.3) 5 (31.3)	 1 (8.3) 0 (0-3) 0 0 4 (33.3) 3 (25.0) 2 (16.7) 4 (33.3)	 0.039 0.0355 0.4921 1.000 - 1.000 0.5604 1.000
WG at COVID-19 onset, median (range)	28 (7-37)	14 (5-30)	0.0234
WG at delivery, median (range)	36 (29-38)	38 (7-42)	0.4111
Type of delivery, N (%) Cesarean section Vaginal	 11 (68.6) 4 (25.0)	 4 (33.3) 4 (33.3)	 -
Preeclampsia, N (%)	1 (2.3)	2 (16.7)	-
COVID-19 period	10/03/2020 to 25/02/2022	23/02/2020 to 29/03/2022	-
Variant period, N (%) Alpha Delta Omicron	 10 (62.5) 1 (6.3) 5 (31.3)	 6 (50.0) 0 6 (50.0)	 0.7022 1.000 0.441
Length of hospital stay in days, median (range)	6 (1-54)	NA	-
VOE during hospitalization, N (%) ACS Vaso-occlusive crisis	 2 (12.5) 6 (37.5)	 NA NA	 - -
Patients in ICU, N (%)	5 (31.3)	NA	-
Length of stay in the ICU in days, median (range)	8 (3-30)	NA	-

BMI: body mass index; ACS: acute chest syndrome; COVID-19: coronavirus disease 2019; WG: weeks of gestation; NA: not applicable; VOE: vaso-occlusive events; ICU: Intensive Care Unit.

and 5 late preterm) and only ten births (43.5%) at term (≥37 WG). Fifteen patients (65%) had a Cesarean section: the indications were elective Cesarean section (details not provided, n=7), pre-eclampsia or "hemolysis, elevated liver enzymes and low platelets" (HELLP) syndrome (n=3), acute fatty liver of pregnancy (n=1), fetal heart rate abnormality (n=3), and placenta previa (n=1). The obstetric complications notably included pre-eclampsia in three patients, HELLP syndrome in one, and posterior reversible encephalopathy syndrome in another (Table 2).

During pregnancy, the known changes in the immune system and cardiopulmonary physiology are likely to have an impact on the risk of severe infectious diseases, including COVID-19, especially in at-risk populations, such as women with SCD. Our present results highlight the elevated maternal and fetal morbidity rates in 28 infected pregnant women with SCD – especially when the infection occurred during the second and third trimesters. Although not statistically significant, the risk of hospital admission for SC women with COVID-19 appeared to be very high (71%). The only death concerned a unvaccinated woman with an SC genotype; Arlet *et al*. had already highlighted the elevated mortality rate associated with the HbSC genotype.[3] Studies of the general population have revealed an elevated ICU admission rate among pregnant women with COVID-19 (odds ratio: 2.13) and a greater risk of death (adjusted risk ratio: 1.7-1.8), when compared with that of nonpregnant women of reproductive age.[6,7] These risks appear to be higher still in women with SCD and depend on the variant of SARS-CoV-2. The severity of COVID-19 is also related to the variant: in the general population, the hospital admission and ICU admission rates are higher for those infected with alpha and delta variants than for those with the omicron variant (Table 1).[8] Although we noted that all the patients admitted to the ICU were unvaccinated, our small sample size prevented us from drawing conclusions about the efficacy of vaccination.

Given the present study's registry-based design, asymptomatic and non-severe cases of COVID-19 in women with SCD might have been underreported; hence, the impact of vaccination and consequences of COVID-19 might have been

Table 2. Obstetric and fetal outcomes among inpatients and outpatients.

Period of delivery	Inpatients, N=16							Outpatients, N=12				
	GA at COVID-19 diagnosis (WG+d)	ICU	Genotype	LOS in hospital (d)	GA at delivery (WG+d)	Obstetric outcomes	Fetal outcomes	GA at COVID-19 diagnosis (WG+d)	Genotype	GA at delivery (WG+d)	Obstetric outcomes	Fetal outcomes
<22 WG	-	-	-	-	-	-	-	5	S-β$^+$	7	Miscarriage	-
Extremely preterm	-	-	-	-	-	-	-	8	SS	27 + 4	-	IUGR, FHR anomaly
Very preterm	28* 30 28	Yes Yes Yes	SC SC SS	20 53 54	29 + 6 31 33 + 5	- - HMD	-	17	SS	31	-	FHR anomaly
Moderately preterm	7 32	No No	SS SC	5 4	33 + 6 34 + 5	- -	HMD PROM	6	SC	35 + 5	-	-
Late preterm	34 35 26 7	Yes No No No	SS S-β^0 SS SC	14 16 2 NP	35 35 + 5 36 + 1 36 + 4	HELLP -	-	-	-	-	-	-
Term	28 37 34 27 10	No No No Yes No	SS SS SS SS SS	3 13 7 6 1	37 37 37 + 1 38 38 + 5	-	FHR anomaly FHR anomaly - IUGR -	2 15 27 30 27	SS SC S-β$^+$ SS SS	38 + 2 39 39 + 1 39 + 1 42	-	-

*Death. Extremely preterm: 22WG to 27WG+6d; Very preterm: 28WG to 31WG+6d; Moderately preterm: 32WG to 34WG+6d; Late preterm: 35WG to 36WG+6d; Term: ≥37WG; GA: gestational age; COVID-19: coronavirus disease 2019: WG: weeks of gestation; d: days; ICU: Intensive Care Unit; LOS: length of stay; IUGR: intrauterine growth retardation; FHR: fetal heart rate; HELLP: hemolysis, elevated liver enzymes and low platelets; HMD: hyaline membrane disease; PROM: premature rupture of membranes.

overestimated. In contrast to other studies, the small size of our subgroups prevented us from substantiating the harmful influence of the SC genotype.

In our cohort, the incidence of obstetric complications (especially preeclampsia) was strikingly high – even for an SCD population. COVID-19 is reportedly associated with a higher incidence of preeclampsia in women in the general population (11%)[9,10] and preeclampsia is also more frequent in women with SCD.[5] The risks of maternal mortality and morbidity are substantial in SCD, both in the SS and SC genotypes.[5] In a recent study of data extracted from the French National Healthcare Data System (*Système National des Données de Santé*) between 2013 and 2020, we estimated that the incidence of preeclampsia was 9.6% in pregnant women with SCD and 1.7% in pregnant women in the general population. Not unexpectedly, the concomitant presence of two risk factors (SCD and COVID-19) is harmful and might explain the two occurrences of rare, severe complications of pregnancy (HELLP syndrome and one posterior reversible encephalopathy syndrome) in our study. Preterm deliveries were also more frequent in our cohort than in pregnant women with SCD in general; these deliveries were directly linked to COVID-19 in three inpatients (10.7% of the study population) and concomitant with COVID-19 in another inpatient (3.6%). The frequency of preterm delivery is nearly three times higher among women with SCD (~20%)[11] than in the general population. Interestingly, the preterm birth rate among women infected by SARS-COV-2 in the general population (11%) is substantially lower than the value in our cohort (54%).[12] We noted a correspondingly high incidence of Cesarean sections, around 65% in our cohort, compared with 30% to 40% in pregnant women with SCD in the literature.[13] The literature data in this field are very limited: we found only one retrospective report on good fetal outcomes in a small (n=8) cohort of women with SCD and COVID-19.[14]

The severity of COVID-19 among women with SCD appears to be linked to destabilization of the latter, rather than a direct effect of the SARS-CoV-2 infection: acute chest syndrome was the main aggravation of SCD, and no cases of severe respiratory disease linked to COVID-19 were observed.

We found that the proportion of SCD women vaccinated against COVID-19 was low: around 31%. It is well known that there is a reluctance among SCD patients to be vaccinated. In our SCD cohort from a sickle cell center in Paris, only 48.9% were vaccinated against COVID-19; this is much lower than the value of 72.3% observed for the age group 18-39 years in the general population.[15] During pregnancy, a fear of harming the fetus might add to ethnic and cultural factors, resulting in an estimated vaccination rate around 65.7%, which is lower than that in the general population.[16]

In conclusion, our results emphasize the need to monitor and manage COVID-19 during pregnancy carefully, particularly in women with SCD. The fact that the only death in our cohort concerned a woman with the SC genotype might be a warning sign. Vaccination should be especially recommended in these women, who are particularly at risk of severe obstetric and fetal complications. The COVID-19 pandemic is not over and so the possible impacts of future variants must be closely monitored.

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Contributions

All authors followed up patients, interpreted data, revised the manuscript for critical content, and approved the final manuscript. SMan analyzed the data.

Data-sharing statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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