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CLINICAL ARTICLE

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# Impact of prenatal corticosteroid therapy on sickle cell disease in pregnant women

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## Abstract

**Objective:** To evaluate safety of prenatal corticosteroids in pregnancies of women with sickle cell disease.

**Methods:** A multicenter observational study of patients with sickle cell disease, comparing vaso-occlusive crises (VOC) requiring hospital care between pregnancies with versus without prenatal corticosteroids.

**Results:** In 40 pregnancies exposed to prenatal corticosteroids, compared with 370 unexposed pregnancies, VOC were not more frequent (62.5% vs 57.9%, $P=0.578$) but they were more severe, with more intensive care hospitalizations (25.0% vs 12.9%, $P=0.039$), emergency transfusions (44.7% vs 22.7%, $P=0.006$), and acute chest syndromes (22.5% vs 8.9%, $P=0.010$). These differences persisted after adjustment for severity and type

of sickle cell syndrome (for intensive care admission adjusted odds ratio [aOR] 2.73, 95% confidence interval [CI] 1.10–6.79, $P=0.031$ and for acute chest syndrome aOR 4.15, 95% CI 1.57–14.4, $P=0.008$). VOC occurred on average 1.2 days following steroid administration. When comparing 36 patients receiving corticosteroids for fetal maturation with 58 patients who were hospitalized for obstetrical complications before 34 weeks of pregnancy but that did not receive corticosteroids, VOC incidence was not significantly higher (41.7% vs 31.5%, $P=0.323$).

**Conclusion:** The present study was the first to study the impact of prenatal corticosteroids on sickle cell disease. They were associated with more severe VOC, suggesting that steroids should be avoided in these women.

**KEYWORDS**
pregnancy, prenatal corticosteroids, preterm birth, sickle cell disease, vaso-occlusive crisis

## 1 | INTRODUCTION

Sickle cell disease (SCD), one of the most common genetic diseases, is a major health problem worldwide. Pregnancies involving SCD are at increased risk of ending in fetal death and maternal death, which remains around 1% in high-resource settings despite improved management,[1] because of pregnancy complications and SCD complications.[2–6] Maternal complications include vaso-occlusive sickle cell crisis (VOC), acute chest syndrome (ACS), pre-eclampsia, thromboembolism, and infections. The main perinatal complications are preterm delivery, with an incidence of 9%[7] to 23%,[8,9] intrauterine growth restriction (IUGR) and fetal death.[2–5,10–13]

In women at high risk of spontaneous or medically indicated preterm birth before 34 weeks of pregnancy, prenatal corticosteroids (PC) are recommended (Collège national des gynécologues et obstétriciens français, 2016 Guideline #20209), because they are beneficial to prevent neonatal mortality, hyaline membrane disease, intraventricular hemorrhage, and ulcerative necrotizing enterocolitis.[14]

However, there is concern that the use of corticosteroids in patients with SCD may trigger VOC.[1] There has been no study to date and no guideline, so corticosteroid use differs between countries and centers. Some experts avoid corticosteroids and consider prophylactic transfusion to decrease the risk of VOC.[1,15]

Our objective was to determine whether there is an association between PC therapy and VOC in pregnant women with SCD.

## 2 | MATERIALS AND METHODS

The Drepagest study was a retrospective multicenter observational study of obstetrical management in women with SCD in centers in metropolitan France and Martinique. All participating maternity units are associated with a competence or reference center for SCD. All patients received the usual care as defined in each center.

### 2.1 | Study population

All patients delivering in the centers between January 1, 2009 and June 30, 2020 at 23 weeks of pregnancy or more, having a major sickle cell syndrome (homozygous S/S, S/C, or S/β-thalassemia) were included. For patients with more than one eligible pregnancy during the period, we included either the first pregnancy or the first with corticosteroid use.

### 2.2 | Outcomes

The main outcome was the occurrence during pregnancy of a VOC (an acute episode of pain in bones and muscle or joints in the absence of a traumatic or other cause) requiring emergency hospital care. Secondary outcomes were the number of VOC during pregnancy, VOC requiring opioids, hospitalizations in intensive care for VOC, ACS, thromboembolic complications, preterm deliveries before 37 weeks of pregnancy and neonatal complications (death, hyaline membrane disease, intraventricular hemorrhage, and/or ulcerative necrotizing enterocolitis).

### 2.3 | Variables

We collected baseline socio-demographic and clinical characteristics, SCD type (S/S, S/C or S/β) and severity of the disease. Severe SCD was defined by one or more of the following criteria: admission to an intensive or critical care unit, ACS, more than three VOC requiring hospitalization over a 1-year period, frequent VOC with personal or social impact, organ damage. Pregnancy complications, prenatal corticosteroid therapy and management, delivery, postpartum and neonatal outcomes were also collected.

### 2.4 | Statistical methods

Since the impact of PC on SCD complications has not been previously published, we could not estimate the number of participants needed to demonstrate a difference in the outcome. Qualitative variables were described and analyzed by comparing the proportions in each group using a $\chi^2$ test or Fisher exact probability as appropriate. Quantitative variables were compared Student *t* test. Multivariate analyses were performed by logistic regression. The threshold of statistical significance was set at a *P* value less than 0.05. We performed sensitivity analyses restricting the study population to women eligible for PC before 34 weeks of pregnancy. Propensity scores were used to estimate the probability of receiving PC. Finally, we studied factors associated with the occurrence of VOC among women receiving PC. Patient records were integrated into an anonymized database via the REDCAP secure database management application[16] and analyzed retrospectively using XLSTAT and STATA 14 (StataCorp LLC, College Station, TX, USA).

### 2.5 | Ethical aspects

The study was performed in accordance with the principles of the Helsinki Declaration. All patients gave approval for use of their medical records, and the study was approved by the Institutional Review Board.

## 3 | RESULTS

### 3.1 | Description of the population

We included 410 pregnancies with SCD. The majority had S/S type SCD ($n=248$; 60.5%), 213 (51.9%) had a history of severe SCD as defined, and 55 (13.4%) had a history of thromboembolism. During the pregnancy, 189 patients (46.1%) received scheduled transfusions. Regarding SCD complications during pregnancy, 233 (56.8%) patients had one or more VOC, 42 (10.2%) had an ACS and 11 (2.7%) had a deep vein thrombosis or pulmonary embolism, including two bilateral pulmonary embolisms. Sixty-two (15.1%) patients had infections (including 18 pulmonary infections and 8 with pyelonephritis). In all, 154 patients (37.5%) had pregnancy-related complications, including 54 with IUGR (13.2%), 53 with pre-eclampsia (12.9%), and seven with chorioamnionitis (1.7%). There were 244 (59.5%) cesarean deliveries. Among 434 liveborn infants, 32 (7.4%), all preterm, had neonatal complications, mostly hyaline membrane disease.

### 3.2 | Comparison of pregnancies exposed or unexposed to PC

Forty patients (9.8%) received PC for fetal lung maturation, all with a single course of betamethasone; none received dexamethasone. Their body mass index was lower than that of patients not receiving PC ($P=0.039$). Other variables were similar between the two groups, including SCD type and severity, and management (medications, anticoagulants, prophylactic oxygen, transfusion programs) (Table 1). All of the patients were hospitalized for a high risk of preterm birth. Two of the patients in the group who received corticosteroids had non-severe VOC before administration; both of them became severe within a few hours and required transfer to intensive care on day 1 and day 2, respectively.

There was no significant difference in the incidence of VOC requiring hospital care (62.5% vs 57.9%, respectively, $P=0.578$), but patients exposed to PC had twice as many severe VOC requiring admission to intensive care (25.0% vs 12.9%, $P=0.039$), emergency transfusions for VOC (44.7% vs 22.7%, $P=0.006$) and ACS (22.5% vs 8.9%, $P=0.010$). These differences persisted after adjustment for severity of SCD and type of sickle cell syndrome (for admission to intensive care for VOC, adjusted odd ratio [aOR] 2.73, 95% confidence interval [CI] 1.10–6.79, $P=0.031$; and for ACS, aOR 4.15, 95% CI 1.57–14.4, $P=0.008$). The incidence of thrombosis was higher without attaining significance (7.5% vs 2.3%, $P=0.059$) (Table 2).

Women exposed to PC had more hospitalizations before 34 weeks for obstetrical complications than unexposed patients, notably preterm labor (30.0% vs 1.6%; $P<0.001$), reflecting the indication for lung maturation. Over half of the PC-exposed women delivered before 34 weeks of pregnancy (57.5% vs 6.8% of the unexposed, $P<0.001$), mostly by emergency (unplanned) cesarean section (72.5% vs 42.1%, $P<0.001$) (Table 3). The indication for cesarean section was VOC or ACS in 17.5% of cases versus 7.8% ($P=0.039$). Other indications for cesarean were pre-eclampsia, pulmonary embolism, severe hemolytic anemia, or severe sepsis. Postpartum maternal intensive care was required in 25.0% versus 10.1% ($P=0.005$), mainly for severe VOC/ACS. PC-exposed newborns were also, as expected, more often preterm, with more neonatal complications (33.3% vs 4.4%, $P<0.001$) (Table 3). Seven patients receiving PC delivered after 34 weeks of pregnancy, and all had severe sickling crises.

We then restricted the analysis to patients receiving PC for obstetrical reasons ($n=36$) and compared them to the unexposed who were potentially eligible for PC, i.e. patients hospitalized before 34 weeks at risk of induced or spontaneous preterm delivery ($n=58$).

Patients who were eligible but unexposed, in comparison with PC-exposed patients, were more often S/S type (47/58 [82.5%] vs 19/36 [52.8%], $P=0.01$) (Table S1) and had more VOC before hospitalization (30/58 [68.8%] vs 10/36 [27.8%], $P=0.004$) (Table 4), but did not have more SCD complications during the pregnancy before hospitalization (Table 4). The PC-exposed were more often hospitalized for threatened preterm labor (12/58 [33.3%] vs 6/36 [10.3%], $P=0.009$; Table 4).

During hospitalization, the incidence of VOC after PC was 41.7%, versus 31.5% for the PC-eligible unexposed, and VOC requiring opioids, ACS or hospitalization in ICU did not differ significantly. Because there was a possible selection bias, we performed

**TABLE 1** Baseline characteristics of pregnancies according to exposure to prenatal corticosteroid therapy.[a]

| Characteristics | Prenatal corticosteroids ($n=40$) | | No prenatal corticosteroids ($n=370$) | | |
|---|---|---|---|---|---|
| | *n* | % | *n* | % | *P* value |
| Demographics and medical history | | | | | |
| Maternal age at delivery | 30.9 | ±6.0 | 29.6 | ±5.4 | 0.109 |
| Geographical origin | | | | | |
| Sub-Saharan Africa | 30 | 75.0% | 280 | 75.7% | 0.677 |
| Caribbean | 6 | 15.0% | 59 | 15.9% | – |
| Other | 4 | 10.0% | 23 | 6.2% | – |
| Missing | 0 | 0% | 8 | 2.2% | – |
| Body mass index | 24.2 | ±6.4 | 23.1 | ±4.6 | 0.140 |
| Undernourished (BMI <18.5) | 4 | 10.0% | 33 | 9.1% | 0.039 |
| Normal (BMI 18.5–24.9) | 18 | 45.0% | 236 | 64.8% | – |
| Overweight (BMI 25–29.9) | 11 | 27.5% | 68 | 18.7% | – |
| Obesity (BMI ≥30.0) | 7 | 17.5% | 27 | 7.4% | – |
| Smoking | 1 | 2.6% | 9 | 2.2% | 1 |
| Nulliparity | 27 | 67.5% | 194 | 52.4% | 0.070 |
| Twin pregnancy[b] | 5 | 12.5% | 19 | 5.1% | 0.070 |
| Comorbidity[c] | 10 | 25.0% | 111 | 28.1% | 0.671 |
| Diabetes | 0 | 0% | 1 | 0.3% | 1 |
| Cardiovascular | 3 | 7.5% | 31 | 8.4% | 1 |
| Respiratory | 1 | 2.5% | 18 | 4.9% | 1 |
| Neurologic | 2 | 5.0% | 17 | 4.6% | 1 |
| Renal | 1 | 2.5% | 10 | 2.7% | 1 |
| Other | 5 | 12.5 | 49 | 13.3 | 0.877 |
| Thromboembolic history | 6 | 15.0 | 43 | 11.8 | 0.556 |
| Sickle cell disease history | | | | | |
| Type of SCD | | | | | |
| SS | 22 | 55.0% | 226 | 61.6% | 0.688 |
| Sβ | 5 | 12.5% | 43 | 11.7% | – |
| SC | 13 | 32.5% | 98 | 26.7% | – |
| Hemoglobin concentration at baseline, g/dL | 8.9 | ±1.6 | 9.0 | ±1.4 | 0.761 |
| Severe SCD[d] | 25 | 62.5% | 188 | 51.8% | 0.201 |
| History of transfusion | 34 | 85% | 288 | 80.9% | 0.532 |
| History of transfusion complications[c] | 8 | 20.0% | 43 | 12.3% | 0.170 |
| Allo-immunization | 4 | 10.0% | 25 | 7.1% | 0.521 |
| Delayed hemolysis | 2 | 5.0% | 15 | 4.3% | 0.688 |
| Hemochromatosis | 2 | 5.0% | 7 | 2.0% | 0.225 |
| Infection | 0 | 0% | 3 | 0.85% | 1 |
| Pregnancy-related diseases | | | | | |
| Hospitalization for obstetrical complications before 34 weeks | 36 | 90.0% | 58 | 15.7% | <0.001 |
| Preeclampsia | 13 | 32.5% | 40 | 10.9% | <0.001 |
| Severe pre-eclampsia | 9 | 22.5% | 20 | 5.4% | <0.001 |
| Gestational diabetes | 3 | 7.5% | 17 | 4.7% | 0.430 |
| Intrauterine infection | 2 | 5.0% | 6 | 1.6% | 0.139 |
| Bacterial infection | 12 | 30.0% | 51 | 13.8% | 0.008 |
| Cervical cerclage | 2[e] | 5.0% | 2[f] | 0.5% | 0.039 |

TABLE 1 (Continued)

| Characteristics | Prenatal corticosteroids (*n* = 40) | | No prenatal corticosteroids (*n* = 370) | | |
|---|---|---|---|---|---|
| | *n* | % | *n* | % | *P* value |
| Threatened preterm labor | 12 | 30.0% | 6 | 1.6% | <0.001 |
| PPROM | 6 | 15.0% | 9 | 2.4% | <0.001 |
| IUGR | 14 | 35.0% | 40 | 10.9% | <0.001 |
| Severe IUGR <3rd centile | 5 | 12.5% | 18 | 4.9% | 0.029 |
| Fetal malformative or genetic disease | 1 | 2.5% | 12 | 3.2% | 1 |
| Postpartum period | | | | | |
| PPH | 9 | 22.5% | 57 | 15.7% | 0.27 |
| Severe PPH | 4 | 10.0% | 22 | 5.9% | 0.32 |
| Admission to ICU/critical care | 10 | 25.0% | 37 | 10.1% | 0.005 |
| Indication for ICU admission[b] | | | | | |
| VOC/ACS | 7 | 17.5% | 25 | 6.8% | 0.019 |
| Hypertensive complication | 2 | 5.0% | 7 | 1.9% | 0.217 |
| PPH | 1 | 2.5% | 10 | 2.7% | 1 |
| Other | 5 | 12.5% | 12 | 3.3% | 0.020 |

Abbreviations: ACS, acute chest syndrome; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); ICU, intensive care unit; IUGR, intrauterine growth restriction; PC, prenatal corticosteroids; PPH, postpartum hemorrhage; PPROM, preterm prelabor rupture of membranes; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

[a]Data are presented as mean ± standard deviation or as number and percentage.

[b]All twin pregnancies were dichorionic.

[c]They are not mutually exclusive.

[d]Severe sickle cell disease defined by the existence of one or more of the following criteria: history of hospitalization in ICU or in ICU for VOC, history of ACS, history of more than three VOC requiring hospitalization over 1 year, frequent VOC with impact on personal life, visceral damage.

[e]One patient had a prophylactic cerclage, the other one had a therapeutic cerclage.

[f]Both had a prophylactic cerclage.

an adjustment on the propensity score estimating the probability of receiving PC. The propensity score-adjusted results did not differ from the primary results, and the ORs associated with the main outcomes were further attenuated (Table 5).

Over half of the patients in both groups delivered by emergency cesarean section, with no significant difference in the indications between the two groups. More than half of cesarean sections were performed before 34 weeks (61.1% vs 27.6%, $P = 0.012$). There were more neonatal complications in the PC group (33.3% vs 13.8%, $P = 0.004$), related to the difference in gestational age (Table 6).

Finally, we sought to determine characteristics associated with the occurrence of VOC after PC (Table 7). The risk of VOC was higher in severe baseline SCD (OR 6.0, 95% CI 1.47–31.6, $P = 0.023$). The proportion with S/S disease was higher, without reaching statistical significance (Table S2). The number of VOC during pregnancy, management of SCD during pregnancy and pregnancy-related diseases did not differ, except for IUGR, which was more frequent than in patients who did not have VOC following PC (9/18 [50.0%] vs 4/22 [18.2%]; $P = 0.050$).

Seven patients received prophylactic exchange transfusions 24–48 h before PC. Among them, three developed VOC. Exchange transfusion was not associated with a reduced risk of VOC among PC patients. One patient received oral prednisone 10 mg/24 h twice before PC with the objective of corticosteroid desensitization, but she developed severe VOC.

The time between PC and the onset of VOC was a mean of 1.2 days (±1.3 days standard deviation). Two patients had bilateral pulmonary embolisms within 24 h of PC.

In multivariate analysis, adjusted for the severity of SCD, the occurrence of VOC after PC was not significantly reduced in case of transfusion or other prophylaxis before PC (Table 8).

## 4 | DISCUSSION

Patients exposed to prenatal corticosteroids had more severe VOC and more ACS. They also tended to have more thromboembolic complications. However, the overall incidence of VOC among women with SCD receiving PC was not higher than in those who did not receive steroids. When comparing pregnancies exposed to PC with patients also hospitalized before 34 weeks of pregnancy at risk of preterm delivery we did not find any significant difference in outcomes, even after adjustment on the propensity score. These results should nevertheless be taken with caution because few eligible patients received steroids, which is consistent with a restrictive approach in clinical practice in France. The timing of events could

**TABLE 2** Sickle cell disease complications during pregnancy according to exposure to prenatal corticosteroid therapy.[a]

| | Prenatal corticosteroids ($n=40$) | | No prenatal corticosteroids ($n=370$) | | *P* value |
|---|---|---|---|---|---|
| SCD during pregnancy | | | | | |
| Hemoglobin in early pregnancy, g/dL | 9.3 | ±2.8 | 9.1 | ±1.3 | 0.830 |
| Hydroxycarbamide | 2 | 5.0% | 8 | 2.2% | 0.256 |
| Other treatments during pregnancy | | | | | |
| Aspirin | 3 | 7.5% | 35 | 9.5% | 1 |
| LMWH | 5 | 12.5% | 51 | 13.8% | 1 |
| Transfusion program[b] | 20 | 52.6% | 169 | 45.7% | 0.409 |
| Prophylactic oxygen | 5 | 12.5% | 52 | 14.2% | 0.767 |
| SCD complications during pregnancy | | | | | |
| VOC during pregnancy | 25 | 62.5% | 208 | 57.9% | 0.578 |
| Number of VOC during pregnancy | 1.0 | ±1.0 | 1.1 | ±1.4 | 0.349 |
| Emergency transfusion for VOC during pregnancy[c] | 17 | 44.7% | 84 | 22.7% | 0.006 |
| VOC requiring opioids during pregnancy | 20 | 50.0% | 147 | 42.6% | 0.368 |
| Hospitalization in ICU for VOC | 10 | 25.0% | 46 | 12.9% | 0.039 |
| Acute chest syndrome during pregnancy | 9 | 22.5% | 33 | 8.9% | 0.010 |
| Thromboembolic complication during pregnancy | 3 | 7.5% | 8 | 2.3% | 0.059 |

Abbreviations: ICU, intensive care unit; LMWH, low-molecular-weight heparin; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

[a]Data are presented as mean ± standard deviation or as number and percentage.

[b]Transfusion program defined by exchange transfusions at regular intervals during pregnancy.

[c]Does not include transfusions administered as part of a transfusion program or prophylactic transfusions before prenatal corticosteroids.

suggest a role of PC in the occurrence of VOC, which occurred on average 1.2 days following steroid administration.

Vaso-occlusive crises are frequent in pregnant women with SCD, 56.8% in our cohort, similar to other cohorts ranging from 40%[3] to 64.8%,[4] and in a study based on health insurance data where it was 43%.[2] The incidence of ACS was 10.2% in our cohort and between 7% and 20% in previous studies.[4,8,17] The incidence of thromboembolisms was in the order of 3% as in previous studies.[5] There was no maternal death, whereas in previous reports the incidence was around 1%,[1,9] reaching 3% in a meta-analysis by Boafor et al.,[18] which included studies from African countries. The main causes of death were cerebral or pulmonary embolisms.[1,2,4,5]

There are no published data on VOC following corticosteroid use in pregnant women with SCD. In non-pregnant patients with SCD, Bernini et al.[19] and Strouse et al.,[20] showed rates of VOC requiring hospitalization with opioid analgesia within 3–4 days of treatment of 59% and 31.5%, respectively, among patients who received corticosteroids, which is similar to our incidence in pregnant women. The risks and benefits of using corticosteroids in individuals with SCD has recently gained attention. In a meta-analysis, Lopinto et al.[21] were unable to conclude on the benefit of corticosteroids to treat patients hospitalized for VOC or ACS, where the length of hospital stay was reduced when considering three randomized trials, but the risk of readmission increased. The systematic review by Ferreira de Matos et al.[22] concluded that corticosteroid administration to SCD patients results in increased risks of sickling complications. In a population-based retrospective study on 5151 patients, Walter et al.[23] found that corticosteroid exposure was associated with the occurrence of hospitalizations for VOC in people with SCD (aOR 3.8; 95% CI 2.4–5.6). Interestingly, this association was more frequent in women than men, but the study did not have information on pregnancy status.

The pathophysiologic explanation for why corticosteroid use may favor VOC remains poorly described. It may involve well-known effects of corticosteroids, particularly demargination of granulocytes, osteonecrosis, and immunodepression, with possible exacerbation of an infection;[24,25] two of our patients receiving PC had chorioamnionitis after preterm prelabor rupture of membranes.

Poor neonatal outcomes in the group receiving PC were related to preterm deliveries before 34 weeks, which occurred in over 60% in this group, over twice the rate in the patients not receiving PC, which reflects the indications for fetal pulmonary maturation.[26]

In view of the risks, we suggest that PC should be avoided.[14] The risk of VOC after PC, and of severe manifestations, was highest among patients with severe S/S SCD and when the indication for PC was IUGR. However, no element was completely predictive of safety of PC.

When corticosteroids are required in a patient with SCD, some experts recommend using preventive measures prophylactically, such as hydroxyurea and/or transfusion.[22] We could not demonstrate protection from VOC after PC using exchange transfusions or oxygen, however statistical power was very limited. There was a trend not attaining statistical significance towards more transfusions before corticosteroids, compared with patients eligible for but not treated with corticosteroids. Transfusion programs have

**TABLE 3** Perinatal outcomes in patients with sickle cell disease according to exposure to prenatal corticosteroid therapy.[a]

| | Prenatal corticosteroids ($n=40$) | | No prenatal corticosteroids ($n=370$) | | *P* value |
|---|---|---|---|---|---|
| Obstetrical outcomes | | | | | |
| Gestational age at delivery, weeks | 32.4 | ±3.9 | 35.2 | ±3.0 | <0.001 |
| Before 34 weeks | 22 | 57.5% | 25 | 6.8% | <0.001 |
| Between 34 weeks and 37 weeks | 11 | 27.5% | 77 | 20.8% | – |
| After 37 weeks | 6 | 15.0% | 268 | 72.4% | – |
| Hemoglobin rate at delivery, g/dL | 8.7 | ±1.9 | 9.0 | ±1.5 | 0.349 |
| Delivery | | | | | |
| Vaginal delivery | 7 | 17.5% | 158 | 42.8% | 0.001 |
| Emergency cesarean section | 29 | 72.5% | 155 | 42.1% | – |
| Scheduled cesarean section | 4 | 10.0% | 56 | 15.2% | – |
| Indication for cesarean section[b] | | | | | |
| Fetal distress | 12 | 30.0% | 36 | 24.8% | 0.509 |
| IUGR | 9 | 22.5% | 12 | 3.2% | <0.001 |
| Macrosomia | 0 | 0% | 1 | 0.3% | 1 |
| Pre-eclampsia | 9 | 22.5% | 26 | 7.0% | 0.001 |
| VOC/ACS | 7 | 17.5% | 29 | 7.8% | 0.039 |
| Failed labor induction | 1 | 2.5% | 43 | 11.6% | 0.058 |
| Scarred uterus | 8 | 20.0% | 30 | 20.7% | 0.918 |
| Other | 12 | 30.0% | 50 | 13.5% | 0.010 |
| Neonatal outcomes ($n=434$ with twins) | ($n=45$) | | ($n=389$) | | |
| Vital status | | | | | |
| Liveborn | 42 | 93.3% | 380 | 97.7% | 0.697 |
| Stillborn | 2 | 4.4% | 4 | 1.0% | – |
| Intrapartum death | 1 | 2.2% | 0 | 0% | – |
| Neonatal death | 0 | 0% | 1 | 0.3% | – |
| Termination of pregnancy | 0 | 0% | 4 | 1.0% | – |
| Birth weight, g | 1693.3 | ±749.3 | 2713.9 | ±685.5 | <0.001 |
| Percentile | 22.3 | ±26.5 | 32.0 | ±28.0 | 0.029 |
| Arterial pH | 7.27 | ±0.1 | 7.27 | ±0.1 | 0.847 |
| Median 5-minute Apgar | 8 | ±2 | 9 | ±1 | <0.001 |
| Neonatal complications | 15 | 33.3% | 17 | 4.4% | <0.001 |
| Type of neonatal complications[b] | | | | | |
| Hyaline membrane disease | 15 | 33.3% | 16 | 4.1% | <0.001 |
| Intraventricular hemorrhage | 2 | 4.4% | 0 | 0% | 0.010 |
| Ulcerative necrotizing enterocolitis | 1 | 2.2% | 1 | 0.3% | 0.166 |

Abbreviation: ACS, acute chest syndrome; IUGR, intrauterine growth restriction; VOC, vaso-occlusive crisis.

[a]Data are presented as mean ± standard deviation, or as number and percentage; unless otherwise stated.

[b]They are not mutually exclusive.

been found to be effective in reducing VOC and ACS,[15] but there is ongoing controversy. Transfusions can lead to alloimmunization, acute or delayed hemolysis, as observed in our cohort.[3,6,12,27,28] French recommendations,[15] based on the work of Howard et al.[8] and Koshy et al.,[29] recommend restricting transfusions in pregnancy to patients with pre-existing severe organ damage (renal failure, cardiac insufficiency) or with severe or repeated VOC or ACS during the pregnancy. Prophylactic transfusions before PC administration are recommended by Habibi[15] and the French Health Authority[15] in order to limit the risk and severity of VOC, although previous studies did not include pregnant patients.[30–32]

Hydroxyurea or hydroxycarbamide is usually contraindicated in the first trimester of pregnancy and is generally avoided throughout pregnancy because of the risk of bone marrow suppression.[12,33] Hydroxyurea at conception and during pregnancy was associated with a two-fold increase in miscarriage and stillbirth[34] and increased

**TABLE 4** Comparison of the patients receiving prenatal corticosteroids with patients hospitalized during pregnancy who were eligible for fetal maturation, but did not receive corticosteroids.[a]

| | Exposed to prenatal corticosteroids ($n=36$) | | Eligible for, but not exposed to prenatal corticosteroids ($n=58$) | | *P* value |
|---|---|---|---|---|---|
| Baseline data on SCD | | | | | |
| Hemoglobin rate in early pregnancy, g/dL | 9.3 | ±0.19 | 8.7 | ±1.4 | 0.998 |
| Long-term treatment | | | | | |
| Hydroxycarbamide | 2 | 5.6% | 3 | 5.2% | 1 |
| Erythropoietin | 0 | 0% | 1 | 1.7% | 1 |
| Other treatment during pregnancy[b] | | | | | |
| Aspirin | 2 | 5.6% | 10 | 17.2% | 0.125 |
| LMWH | 5 | 13.9% | 10 | 17.2% | 0.642 |
| Transfusion program[c] | 20 | 58.8% | 23 | 39.7% | 0.099 |
| Emergency transfusion for VOC[d] | 14 | 41.2% | 17 | 29.3% | 0.249 |
| Prophylactic oxygen therapy | 5 | 13.9% | 6 | 10.5% | 0.755 |
| VOC | 10 | 27.8% | 30 | 68.8% | 0.004 |
| VOC requiring opioids | 5 | 13.9% | 24 | 48.0% | 0.001 |
| Hospitalization in ICU for VOC | 2 | 5.6% | 8 | 15.7% | 0.190 |
| Acute chest syndrome | 1 | 2.8% | 4 | 6.9% | 0.412 |
| Thromboembolic complication | 0 | 0% | 4 | 6.9% | 0.293 |
| Hospitalization during pregnancy | | | | | |
| Gestational age of PC/of hospitalization | | | | | |
| Before 28 weeks | 14 | 38.9% | 8 | 16.3% | 0.060 |
| Between 28 and 32 weeks | 10 | 27.8% | 18 | 36.7% | – |
| Between 32 and 34 weeks | 12 | 33.3% | 23 | 46.9% | – |
| Indications[b] | | | | | |
| Pre-eclampsia | 13 | 36.1% | 28 | 49.1% | 0.102 |
| Severe preeclampsia | 9 | 25.7% | 17 | 29.3% | 0.531 |
| Intrauterine infection | 2 | 5.6% | 1 | 1.8% | 0.552 |
| Bacterial infection | 11 | 30.6% | 13 | 22.4% | 0.358 |
| Threatened preterm labor | 12 | 33.3% | 6 | 10.3% | 0.009 |
| PPROM | 6 | 16.7% | 4 | 6.9% | 0.163 |
| IUGR | 14 | 38.9% | 28 | 49.1% | 0.448 |
| Severe IUGR <3rd percentile | 5 | 13.9% | 13 | 22.8% | 0.383 |
| Outcomes after PC/after hospitalization | | | | | |
| VOC | 15 | 41.7% | 15 | 31.5% | 0.323 |
| VOC requiring opioids | 12 | 34.3% | 11 | 22.5% | 0.321 |
| VOC requiring ICU hospitalization | 5 | 14.3% | 3 | 6.1% | 0.474 |
| Acute chest syndrome | 4 | 11.1% | 4 | 6.9% | 0.457 |
| Thromboembolism | 1 | 2.8% | 0 | 0% | 0.364 |

Abbreviations: ICU, intensive care unit; IUGR, intrauterine growth restriction; PC, prenatal corticosteroids; PPROM, preterm prelabor rupture of membranes; VOC, vaso-occlusive crisis.

[a]Data are presented as mean ± standard deviation, or as number and percentage.

[b]They are not mutually exclusive.

[c]Transfusion program defined by exchange transfusions at regular intervals during pregnancy.

[d]Does not include transfusions administered as part of a transfusion program or prophylactic transfusions before prenatal corticosteroids.

low birthweight,[34] but there is no evidence of increased congenital anomalies in live-born infants.[34,35] Prophylactic oxygen therapy is being evaluated in a randomized clinical trial based on promising observational data from Ribeil et al.[36]

Pregnancies with major sickle cell syndromes should be managed in reference centers that include obstetricians and anesthesiologists trained in SCD, an adult critical care unit, and a blood transfusion team.

**TABLE 5** Risk of sickle cell crisis adjusted on the probability of receiving prenatal corticosteroids. Comparison of the patients receiving prenatal corticosteroids for fetal maturation with patients hospitalized during pregnancy who were eligible for, but did not receive, corticosteroids.

| Outcome after PC/after hospitalization | OR | 95% CI | aOR[a] | 95% aCI[a] | Adjusted *P* value |
|---|---|---|---|---|---|
| VOC | 1.67 | 0.68–4.08 | 1.37 | 0.43–4.40 | 0.581 |
| VOC requiring opioids | 1.80 | 0.68–4.74 | 1.44 | 0.40–5.11 | 0.842 |
| VOC requiring ICU hospitalization | 2.56 | 0.57–11.49 | 2.20 | 0.2–18.01 | 0.456 |
| Acute chest syndrome | 1.68 | 0.39–7.22 | 1.43 | 0.24–8.60 | 0.682 |

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; PC, prenatal corticosteroids; VOC, vaso-occlusive crisis.

[a]Adjusted on propensity score (probability of receiving prenatal corticosteroids, calculated from the variables body mass index, nulliparity, type of sickle cell syndrome, existence of blood transfusion program, VOC before hospitalization, gestational age at hospitalization, and indication for hospitalization).

**TABLE 6** Comparison of pregnancy and neonatal outcomes in patients receiving prenatal corticosteroids for fetal maturation, compared with patients hospitalized during pregnancy who were eligible for, but did not receive corticosteroids.[a]

| | Exposed to prenatal corticosteroids ($n=36$) | | Eligible for, but not exposed to prenatal corticosteroids ($n=58$) | | *P* value |
|---|---|---|---|---|---|
| Obstetrical outcomes | | | | | |
| Gestational age of delivery, weeks | 32.3 | ±3.9 | 35.2 | ±3.0 | <0.001 |
| Before 32 weeks | 16 | 44.4% | 8 | 13.8% | 0.012 |
| Between 32 and 34 weeks | 6 | 16.7% | 8 | 13.8% | – |
| Between 34 and 37 weeks | 8 | 22.2% | 24 | 41.4% | – |
| After 37 weeks | 6 | 16.7% | 18 | 31.0% | – |
| Neonatal outcomes | | | | | |
| Vital status | | | | | |
| Liveborn | 34 | 94.4% | 57 | 98.3% | 0.14 |
| Stillborn | 2 | 5.6% | 0 | 0% | – |
| Termination of pregnancy | 0 | 0% | 1[c] | 1.7% | – |
| Neonatal complications | 15 | 33.3% | 9 | 15.5% | 0.01 |
| Type of neonatal complications[b] | | | | | |
| Hyaline membrane disease | 15 | 33.3% | 8 | 13.8% | 0.004 |
| Intraventricular hemorrhage | 2 | 4.4% | 0 | 0% | 0.13 |
| Ulcerative necrotizing enterocolitis | 1 | 2.2% | 1 | 1.7% | 1 |

[a]Data are presented as mean ± standard deviation, or as number and percentage.

[b]This patient was admitted at $24^{+3}$ weeks of pregnancy for severe intrauterine growth restriction; an aggravation of fetal Doppler led to a decision to perform termination of pregnancy at $25^{+6}$ weeks.

[c]They are not exclusive of each other.

A randomized trial would be required for definitive proof of whether PC are a risk in pregnant women with SCD but would be challenging because of the number of eligible patients and doubts regarding equipoise. Larger multicenter collaborations could be performed to pool and analyze observational data.

The present study is, to our knowledge, the first to study PC in pregnancies affected by SCD. The large multicenter population allowed for a wide diversity of patients, obstetrical and medical management. We had few missing data for the primary end point, allowing us to take into consideration confounders, construct a propensity score and perform an analysis restricted to women eligible for corticosteroids.

The main weaknesses of the study are the observational nature, leading to treatment bias, and low power to demonstrate causal associations between PC and VOC in the case of obstetrical problems justifying hospitalization before 34 weeks of pregnancy. This was due to the restrictive policy regarding steroids. Also, because of small numbers, we did not differentiate S/$\beta^0$ and S/$\beta$+SCD. Finally, in the case of PC, we could not confirm the impact of prophylactic measures to prevent VOC, for potential treatment bias and lack of power.

**TABLE 7** Among patients receiving prenatal corticosteroids, comparison between those who had sickling crisis following prenatal corticosteroids and those who did not.[a]

| | Patients with VOC ($n=18$) | | Patients without VOC ($n=22$) | | *P* value |
|---|---|---|---|---|---|
| SCD during the pregnancy | | | | | |
| Hemoglobin rate in early pregnancy, g/dL | 9.3 | ±1.2 | 8.5 | ±1.8 | 0.202 |
| Hydroxycarbamide | 0 | 0 | 2 | 9.1 | 0.491 |
| Other treatment during pregnancy | | | | | |
| Aspirin | 1 | 5.6% | 2 | 9.1% | 1 |
| LWMH | 1 | 5.6% | 4 | 18.2% | 0.362 |
| Transfusion program[b] | 7 | 43.7% | 13 | 59.1% | 0.346 |
| Prophylactic oxygen therapy | 1 | 5.6% | 4 | 18.2% | 0.356 |
| Emergency transfusion for VOC[c] | 9 | 56.3% | 8 | 36.4% | 0.221 |
| Prophylactic transfusion before PC | 3 | 16.3% | 4 | 18.2% | 1 |
| Data on VOCs during pregnancy before PC | | | | | |
| VOC before PC | 6 | 33.3% | 7 | 31.8% | 0.920 |
| VOC requiring opioids | 4 | 22.2% | 4 | 18.2% | 1 |
| Hospitalization in ICU for VOC | 3 | 16.7% | 2 | 9.1% | 0.638 |
| Acute chest syndrome | 0 | 0% | 2 | 9.1% | 0.439 |
| Indication for PC[d] | | | | | |
| PPROM | 3 | 16.7% | 2 | 9.1% | 0.644 |
| Preeclampsia | 4 | 12.2% | 7 | 31.8% | 0.723 |
| Risk of preterm labor | 3 | 16.7% | 7 | 31.8% | 0.464 |
| IUGR | 9 | 50.0% | 4 | 18.2% | 0.049 |
| Other | 1 | 5.6% | 3 | 13.6% | 0.609 |
| Gestational age at PC administration, weeks | 29.1 | ±2.8 | 30.0 | ±3.5 | 0.443 |
| Prophylaxis before PC | 4 | 22.5% | 4 | 18.2% | 1 |
| Type of prophylaxis | | | | | |
| Transfusion | 3 | 16.7% | 4 | 18.2% | 1 |
| Prednisone | 1 | 5.6% | 0 | 0% | 0.450 |
| Data on VOCs during pregnancy after PC | | | | | |
| VOC after PC | 18 | 100% | | | |
| VOC requiring opioids | 15 | 88.2% | | | |
| Hospitalization in ICU for VOC | 8 | 47.1% | | | |
| Acute chest syndrome | 7 | 39.9% | | | |
| Thromboembolism | 2 | 11.1% | | | |
| Obstetrical outcomes | | | | | |
| Gestational age at delivery, weeks | | | | | |
| Before 32 weeks | 7 | 38.9% | 7 | 31.8% | 0.940 |
| Between 32 and 34 weeks | 4 | 22.2% | 6 | 27.3% | – |
| Between 34 and 37 weeks | 4 | 22.2% | 6 | 27.3% | – |
| After 37 weeks | 3 | 16.7% | 3 | 13.6% | – |
| Delivery | | | | | |
| Vaginal delivery | 3 | 16.6% | 4 | 18.2% | 0.783 |
| Emergency cesarean section | 14 | 77.8% | 15 | 68.2% | – |
| Scheduled cesarean section | 1 | 5.6% | 3 | 13.6% | – |
| Indication of cesarean[d] | | | | | |
| Fetal distress | 6 | 33.3% | 7 | 31.8% | 0.922 |
| IUGR | 6 | 33.3% | 3 | 13.6% | 0.251 |

TABLE 7 (Continued)

| | Patients with VOC ($n=18$) | | Patients without VOC ($n=22$) | | *P* value |
|---|---|---|---|---|---|
| Preeclampsia | 4 | 22.2% | 5 | 22.7% | 1 |
| VOC/ACS | 6 | 33.3% | 1 | 4.6% | 0.029 |
| Failed labor induction | 0 | 0% | 1 | 4.6% | 1 |
| Scarred uterus | 4 | 22.2% | 4 | 18.2% | 1 |
| Other | 6 | 35.3% | 6 | 27.3% | 0.943 |
| Postpartum complications | | | | | |
| Admission in ICU | 7 | 38.9% | 3 | 13.6% | 0.141 |
| Indication of admission in ICU[d] | | | | | |
| VOC/ACS | 7 | 38.9% | 0 | 0% | 0.007 |
| Hypertensive complication | 2 | 11.8% | 0 | 0% | 0.183 |
| PPH | 0 | 0% | 1 | 4.6% | 1 |
| Other | 3 | 16.7% | 2 | 9.1% | 0.642 |
| Neonatal outcomes | | | | | |
| Vital status | | | | | |
| Liveborn | 18 | 90.0% | 24 | 96.0% | 0.191 |
| Stillborn | 2 | 10.0% | 0 | 0% | – |
| Intrapartum death | 0 | 0% | 1 | 4.0% | – |
| Neonatal death | 0 | 0% | 0 | 0% | – |
| Birth weight, g | 1858.4 | ±649.5 | 1593.9 | ±824.2 | 0.253 |
| Percentile | 26.9 | ±31.6 | 21.2 | ±25.0 | 0.509 |
| Arterial pH | 7.28 | ±0.08 | 7.27 | ±0.1 | 0.708 |
| Median 5-minute Apgar | 7 | ±3 | 8 | ±3 | 0.643 |
| Neonatal complication | 5 | 26.3 | 10 | 41.7% | 0.287 |
| Type of neonatal complications[d] | | | | | |
| Hyaline membrane disease | 5 | 26.3% | 10 | 41.7% | 0.278 |
| Intraventricular hemorrhage | 1 | 5.3% | 1 | 4.2% | 1 |
| Ulcerative necrotizing enterocolitis | 0 | 0% | 1 | 4.2% | 1 |

Abbreviations: ACS, acute chest syndrome; ICU, intensive care unit; IUGR, intrauterine growth restriction; LMWH, low-weight molecular heparin; PC, prenatal corticosteroids; PPH, postpartum hemorrhage; PPROM, preterm prelabor rupture of membranes; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

[a]Data are presented as mean ± standard deviation, or as number and percentage, unless otherwise stated.

[b]Transfusion program defined by exchange transfusions at regular intervals during pregnancy.

[c]Does not include transfusions administered as part of a transfusion program or prophylactic transfusions before PC.

[d]They are not mutually exclusive.

TABLE 8 Association between transfusions before prenatal corticosteroids and occurrence of VOC following prenatal corticosteroids.

| | aOR[a] (95% CI) | *P* value |
|---|---|---|
| Prophylactic transfusion before PC and occurrence of VOC following PC | 1.29 (0.26–6.34) | 0.753 |
| Prophylactic transfusion before PC and occurrence of severe VOC following PC | 0.82 (0.36–9.14) | 0.462 |
| Transfusion programs and occurrence of VOC following PC | 0.55 (0.147–2.07) | 0.371 |
| Transfusion programs and occurrence of severe VOC following PC | 0.68 (0.174–2.68) | 0.572 |

Abbreviations: PC, prenatal corticosteroids; VOC, vaso-occlusive crisis.

[a]Adjusted on severe sickle cell disease.

In conclusion, PC are a risk factor for more severe VOC in patients with SCD, especially in S/S SCD and severe baseline characteristics. Although definitive proof is lacking, we suggest that they should be used only after a multidisciplinary benefit/risk assessment and decision with the patient, when there is a crucial risk of very preterm delivery.

## AUTHOR CONTRIBUTIONS

Laurent Mandelbrot, Florence Wang, and Jeanne Sibiude conceived the study; Florence Wang, Mayi Gnofam, Frédéric Galacteros, Stéphane Bounan, Hervé Fernandez, Axel Fichez, Giovanna Cannas, Marine Driessen, Véronique Debarge, Caroline Makowski, Gylna Loko, and Olivier Graesslin collected, interpreted and analyzed the data; Bassam Haddad performed the statistical analysis; and Florence Wang, Laurent Mandelbrot, Jeanne Sibiude, and Bassam Haddad drafted the manuscript. All authors contributed to writing and approved the final manuscript.

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## CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

## DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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