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RESEARCH ARTICLE

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Transfusion-related adverse events are decreased in pregnant women with sickle cell disease by a change in policy from systematic transfusion to prophylactic oxygen therapy at home: A retrospective survey by the international sickle cell disease observatory

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Abstract

Sickle cell disease (SCD) in pregnancy can be associated with adverse maternal and perinatal outcomes. Furthermore, complications of SCD can be aggravated by pregnancy. Optimal prenatal care aims to decrease the occurrence of maternal and fetal complications. A retrospective, French, two-center study compared two care strategies for pregnant women with SCD over two time periods. In the first study period (2005-2010), the women were systematically offered prophylactic transfusions. In the second study period (2011-2014), a targeted transfusion strategy was applied whenever possible, and home-based prophylactic nocturnal oxygen therapy was offered to all the pregnant women. The two periods did not differ significantly in terms of the incidence of vaso-occlusive events. Maternal mortality, perinatal mortality, and obstetric complication rates were also similar in the two periods, as was the incidence of post-transfusion complications (6.1% in 2005-2010 and 1.3% in 2011-2014, $P = .15$), although no de novo alloimmunizations or delayed hemolysis transfusion reactions were observed in the second period. The results of this preliminary, retrospective

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study indicate that targeted transfusion plus home-based prophylactic nocturnal oxygen therapy is safe and may decrease transfusion requirements and transfusion-associated complications.

1 | INTRODUCTION

Sickle cell disease (SCD) is an inherited disorder caused by a point mutation of the β-globin gene that results in the production of an abnormal β^S-globin. β^S-globin causes hemoglobin S (HbS) to form rigid polymers upon deoxygenation. In turn, the intracellular formation of HbS polymers results in red blood cell (RBC) sickling that leads to the vaso-occlusive crises (VOCs) that are characteristic of SCD. SCD occurs when two copies of the β^S-globin allele (β^S) are present (homozygous β^S genotype, β^S/β^S) and often has a severe clinical presentation. Compound heterozygosity of a β^S-globin allele with another mutation in the β-globin gene (e.g., β^C or β^0) can produce SCD along a broad spectrum of clinical presentations from severe to potentially asymptomatic.

Due to improvements in the management of SCD patients, over 95% of affected infants survive to adulthood in industrialized countries. Therefore, the number of women reaching reproductive age is increasing.[1] In France, more than 300 pregnancies in women with SCD are recorded every year, and pregnancy is known to aggravate the complications of SCD. The maternal risks include prepartum and postpartum VOCs, urinary tract infections, pulmonary complications, anemia, thromboembolic events, hypertensive disorders, and death[2]; these complications may even affect women who only display mild symptoms before pregnancy (including HbSC patients).[3]

Despite the steady decrease in the mortality rate for pregnant women with SCD since the 1970s,[1] several studies over the last two decades have reported poor outcomes for SCD pregnancies.[4] A recent French study showed that between 1996 and 2009, the risk of maternal death was approximately 50 times higher in women with SCD than that in the general population.[5]

The fetal morbidity rate is also higher in women with SCD than that in the general population; fetal growth retardation and induced and spontaneous prematurity are the most common risks. Furthermore, the perinatal mortality rate (up to three months of age) is higher in babies born to women with SCD.[6] The lack of randomized, clinical studies of pregnant women with SCD complicates the development of evidence-based care strategies. Consequently, care is often based on retrospective findings and expert opinions.[7,8]

RBC transfusion and careful prevention of infections represent the only available treatments in this setting. Two different transfusion policies have been proposed. First, prophylactic blood transfusions are intended to provide stable, long-term correction of severe anemia and sickling in both the maternal and placental circulation.[9] Second, therapeutic blood transfusions are initiated only if certain SCD-related adverse events or obstetric complications arise and/or if a woman has a history of organ failure.

The studies that prompted the recommendation of prophylactic transfusions for pregnant women with SCD were biased by the absence of randomization,[10] whereas the only prospective study performed to date failed to show evidence of any benefit for maternal and neonatal outcomes with this strategy (relative to selective transfusion) and concluded that it should not be used without clear indications.[11] In fact, the last study performed in France on systematic prophylactic transfusion in pregnant SCD women showed that the proportion of VOCs was the same as that in patients who were not systematically transfused.[12]

Post-transfusion alloimmunization[13] and delayed hemolytic transfusion reactions (DHTRs) are frequent complications of transfusion during SCD pregnancies that can indirectly affect the newborn by inducing hypoxia and may ultimately prevent the woman from receiving further transfusions.[14,15] Post-transfusion complications represent negative prognostic factors that affect both the mother's health and fetal development, thus increasing the risk of premature death.

Pregnancy outcomes are also complicated by the elevated levels of oxygen required to satisfy the increased metabolic demands of the placenta and fetus. Furthermore, pregnant women are at an increased risk of sleep-disordered breathing (SDB) due to the physiologic changes in pregnancy as evidenced by a high prevalence of snoring in gravidas.

Patients with baseline hypoxemia or asthma have been reported to experience more severe SCA complications[16–19] and (in some studies) pain crises.[16,18,20–22] Interestingly, SDB (including snoring and OSA) has been linked to adverse pregnancy outcomes (such as gestational hypertension[19,23,24] and gestational diabetes)[23,25] and potential adverse fetal outcomes (such as preterm birth[23,24,26] and growth restriction).[27]

Considering these observations, the first innovative approach that we introduced was the widespread use of prophylactic oxygen treatment at home during the night and/or during daytime rest periods. This innovative treatment was initiated based on very preliminary observations in the preceding years, i.e., the clinical benefit observed in some pregnant women with an extensive obstetric history and significant contraindications to transfusion. Moreover, some data in the literature supported our hypothesis and advocated prophylactic oxygen therapy at home,[16,20–22,28–31] as no potential negative impact on erythropoiesis or erythropoietin production was identified.[32,33] This strategy was also prompted by the results of experiments in an SCD mouse model in which a high-oxygen environment during pregnancy was associated with a lower prenatal fetal/maternal mortality rate.[34]

Therefore, the two main objectives of the present retrospective study were to (i) evaluate the potential clinical benefits of the widespread use of prophylactic nocturnal oxygen treatment at home and (ii) identify prognostic factors that influence the complication rate in pregnant women with SCD.

2 | METHODS

We performed a retrospective cohort study based on analysis of electronic and paper-based medical records and hospital admission records. First, we identified pregnant women with SCD who had received

prenatal care at the Department of Biotherapy at Necker Children's Hospital and had given birth at either of the two maternity units/reference centers that manage high-risk pregnancies in the Paris area (Necker Children's Hospital and Antoine Béclère Hospital) between January 2005 and December 2014. Some women had several pregnancies during the study period. Therefore, all the following results are reported with respect to the number of pregnancies, and each pregnancy constituted one case.

After the study protocol had been approved by the local investigational review boards and data protection bodies (*Comité d'Ethique de l'Hôpital Necker-Enfants Malade* (Paris); approved on September 10, 2012; *Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé*; approved on November 15, 2012; *Commission Nationale de l'Informatique et des Libertés*; approved on August 13, 2013), an electronic case report form (e-CRF, available on request) was established for the collection of pre- and postnatal data from prenatal records, hospital admission records, and a database of deliveries at more than 20 WA (estimated from the crown-rump length on the first trimester scan, when available, or the date of the last period). Therefore, elective abortions and unreported, spontaneous abortions were not included in the present survey.

The study database is available on request.

2.1 | Patient care

The care team included a senior hematologist, an obstetrician, an infectious disease specialist, and specially trained midwives. We followed the guidelines issued by the French Reference Center for Major Sickle Cell Syndromes for the care and management of SCD patients.[35] Consultations were scheduled monthly during the first trimester, fortnightly after 24 WA, and weekly after 36 WA. Ultrasound scans were performed at 21–24 WA and between 32–34 WA, as recommended in France. To screen for intrauterine growth retardation (IUGR), two additional scans were performed at 28 and 36 weeks. In the last month of pregnancy, the women were admitted to the obstetric department's day hospital once a week to monitor fetal well-being and plan the delivery. The mode of delivery was selected based on the woman's obstetric history, existing chronic SCD complications, and general condition at the end of pregnancy.

The following data were recorded on the e-CRF for each patient: age, parity, ethnic group, personal medical history (the presence or absence of painful VOCs, acute chest syndrome (ACS), stroke, pulmonary arterial hypertension (PAH, defined as a mean pulmonary arterial pressure of at least 25 mm Hg), or other types of SCD-related chronic organ damage), transfusion history, and obstetric history. Any SCD-related complications during pregnancy were also recorded, along with the number of prenatal visits, any antepartum hospitalizations, and treatments. VOCs necessitating hospitalization, ACS, PAH, acute anemia, splenic sequestration, and other complications of SCD were also recorded, as well as any episodes of pneumonia and urinary tract infections.

The following obstetric parameters were recorded on the e-CRF: preterm delivery, premature rupture of membranes, antepartum hemorrhage, placenta previa, gestational diabetes, oligohydramnios, IUGR, pregnancy-induced hypertension, pre-eclampsia, eclampsia, hemolysis elevated liver enzyme and low platelet count (HELLP) syndrome, intrauterine fetal death (IUFD), stillbirth, uterine rupture, postpartum hemorrhage, chorioamnionitis, breast feeding, and maternal mortality. The type of delivery and any postpartum complications were also noted and analyzed.

Perinatal outcomes included the 5-minute Apgar score, IUGR status (defined as a birth weight below the 10th percentile for gestational age), and perinatal mortality.

Laboratory tests (including the complete blood cell count, an RBC agglutination test, blood and urine biochemistry assays, and a screen for bacteriuria) were repeated at each prenatal visit (or whenever indications appeared) to detect SCD-related, infectious, or obstetric complications. Hemoglobin phenotypes were characterized as SS, SC, SD, or S/beta thalassemia using standard procedures. A fundoscopy and a third-trimester cardiac ultrasound assessment were also scheduled.

The indication for transfusion was selected according to the patient's condition, consistent with the guidelines issued by the French Reference Center for Major Sickle Cell Syndromes (until December 2010)[35] or the UK and US guidelines (from January 2011 onwards).[36] According to the French guidelines for SCD, RBC packs were systematically matched for Rhesus (DCc Ee) and Kell antigens, and then cross-matched with the patient's serum before delivery (to detect any low-frequency antigens). Furthermore, patients presenting with a clinically significant RBC alloantibody were provided with RBC packs lacking the relevant antigen.

Since 2011 (and independently of the transfusion policy), patients have been offered prophylactic oxygen therapy at home (during sleep at night or daytime rest periods; flow rate: 2 to 3 L/min; humidifier if needed) using the Perfecto2™ Series (Invacare, Elyria, Ohio) and Quietlife5 (Airsep Corporation, Buffalo, New York) devices. Oxygen therapy was proposed systematically, even when the patient did not exhibit a low baseline oxygen saturation or nocturnal hypoxia. We used a flow rate of 2 to 3 L/min as this rate is usually recommended for VOCs during hospitalization and is not associated with hypercapnic side effects. We provided nose pieces that were appropriately sized for each patient's face and never used masks. In fact, the minimum oxygen flow rate for a mask is 6 L/min; lower flow rates are associated with insufficient oxygen delivery and increased re-inhalation of carbon dioxide.

The company supplying the home oxygen condenser (VitalAire, Vitry-sur-Seine, France) provided information on the frequency of use (including nights per week, hours per night, and the flow rate). This information was relayed to the patients during a patient education program that included home visits by technicians. The technicians verified the patients' compliance with treatment and safety instructions and helped personalize the device (selection of appropriate nose pieces and humidifiers, etc.). A visit was scheduled every 3 months, and the patient's referring physician always received a copy of the report.

Furthermore, we instructed the patients to use oxygen therapy primarily at night because (i) this is when the upper respiratory tract is most vulnerable congestion and low oxygen saturation, and (ii) we did

not intend to increase the amount of time spent resting during the day, which is not often practical and can also lead to the occurrence of adverse events in pregnant women. We did not perform sleep analyzes before or after the initiation of oxygen therapy.

At each consultation, the patient was asked about her use of prophylactic oxygen therapy at home and was reminded of the treatment instructions.

The following information regarding blood transfusion was recorded: the type of transfusion (prophylactic or, in the event of complications, targeted), pre- and post-transfusion Hb levels, and the mean numbers and volumes of RBC units transfused during pregnancy. Blood transfusion complications, de novo alloimmunization during the current pregnancy, and DHTRs were recorded and reported to the French national drug safety agency (*Agence Nationale de Sécurité du Médicament et des Produits de Santé*). If a woman presented several episodes of a given complication during pregnancy, each episode was recorded separately.

2.2 | Statistical analysis

Treatment-related and obstetric characteristics and maternal and fetal outcomes in the two different time periods were initially compared by applying a chi-squared test or Fisher's test (for categorical variables) or the Mann-Whitney test (for continuous variables). Next, a multivariate logistic regression analysis was performed to estimate the impact of the time period after adjustments for other prognostic factors and/or obstetric complications. The factors that differed significantly between the two groups and all the potential risk factors were included in the final models. The results were expressed as an odds ratio (OR) [95% confidence interval (CI)].

All tests were two-sided. For the determination of factors associated with time-to-event outcomes, the threshold for statistical significance was set to $P < .05$. All the statistical analyzes were performed with SPSS software (version 22, SPSS Inc./IBM, Armonk, New York).

3 | RESULTS

3.1 | Characteristics of the study population

We analyzed 191 cases (pregnancies) in 150 women, with an Hb SS phenotype in 123 cases, an Hb S-β-thalassemia 0 (Sβ0-thal) phenotype in 8 cases, an S-β-thalassemia+ phenotype in 18 cases, an Hb SC phenotype in 39 cases, and an Hb S-Hb D-Punjab phenotype in 3 cases. Seventy-five percent of the cases originated from Sub-Saharan Africa, with 15.2% from the Caribbean, 4.7% from North Africa, and 2.6% from other areas.

The mean (range) age was 30 (15–43) years. Seventy-eight percent of the pregnancies were in the relatively low-risk age group of 18–35 years, with 0.5% under the age of 18 years and 21.5% over the age of 35 years (Supporting Information Table S1). We noted significantly more pregnancies among women aged 35 years or older during the 2011–2014 period.

The pregnant women's medical records confirmed that the study population had an extensive history of severe events: 18.3% of the cases had presented with more than two VOCs requiring hospitalization per year over the previous three years, and 50.8% had presented at least one episode of ACS. We noted all chronic SCD complications that could have influenced the obstetric follow-up or the type of delivery, such as cerebrovascular disease (defined by abnormal transcranial Doppler flow (>170 cm/sec) or overt strokes due to abnormalities in the polygon of Willis),[37] retinopathy,[38] and osteonecrosis in 8.9%, 25.7%, 6.3%, and 19.9% of the pregnancies, respectively (Supporting Information Table S2).

Before pregnancy, 23% of the patients had received a long-term treatment (hydroxyurea (HU) or transfusion (Supporting Information Table S2)); 27% were still receiving HU (Supporting Information Table S2), 16% had discontinued treatment before pregnancy, and 11% had discontinued treatment only when the pregnancy was discovered (after a mean (range) time interval of 10 WA (4–28)). In 17 cases, the patients were on a long-term, prophylactic transfusion regimen (initiated before pregnancy) for SCD complications that was continued during and after pregnancy. More than 14.1% of the cases had a history of transfusion-related complications: 9.4% had developed severe alloimmunization, 6.3% had experienced DHTRs, and 5.8% had a rare blood group.

Voluntary termination of pregnancy was reported for 31.1% of the patients. The obstetric data showed that 23% of the cases were primigravida and 41.9% were nulliparous. The mean (range) gravidity and parity values were 2.97 (1–9) and 0.91 (0–5), respectively. More than 9.4% of the patients had a history of poor obstetric outcomes, with late miscarriage in 2.6% of the patients and IUFD in 6.8% of the patients; however, no perinatal deaths were reported. Cesarean section was reported for 40.4% of the patients who had already given birth (Supporting Information Table S3).

For most of the "maternal history" parameters, no significant changes were observed over the 2005–2010 period or the 2011–2014 period, thus enabling valid interperiod comparisons of outcomes. The patients in 2011–2014, however, were significantly older and less likely to have a history of IUFD. In both periods, the mean (range) number of hematology consultations during pregnancy was 3 (0–10).

3.2 | Pregnancy follow-up, treatment, and morbidity

During the first study period (2005–2010), 115 pregnancies were monitored in our two reference centers (Supporting Information Table S1). Consistent with the French national guidelines, a prophylactic transfusion program was applied in 67% of the cases. Notably, prophylactic transfusion was contraindicated in 13% of the cases.

A targeted transfusion strategy was applied during the second study period (2011–2014), consistent with the UK and the US guidelines. Furthermore, prophylactic oxygen therapy at home was offered to all the pregnant women with SCD. At each medical consultation, the women were asked whether they were adhering to this treatment; 84.2% stated that they were, and this finding was confirmed by the data provided by the device provider. Data regarding oxygen therapy were available for 45% of the cases during the 2011–2014 period. The mean flow rate was 2.7 L/min, and the median duration of use was 129 min (range: 1–685). During the 2011–2014, 40.8% of the cases participated in a prophylactic transfusion program ($P = .0002$).

TABLE 1 SCD-related maternal complications

Period	2005–2010	2011–2014	Total	*P*
ß-hemoglobin level, g/L (range)	9.5 (5.6–12.5)	8.9 (6.9-7.75)	9.25 (5.6–12.5)	.005
Pregnancies	*n* = 115 (60.2%)	*n* = 76 (39.8%)	*n* = 191 (100%)	-
Two or more transfusions	75 (65.2%)	27 (35.5%)	102 (53.4%)	.00006
Post-transfusion complications	7 (6.1%)	1 (1.3%)	8 (4.2%)	.15
De novo alloimmunization	3 (2.6%)	0 (0%)	3 (1.6%)	.28
Delayed hemolytic transfusion reaction	4 (3.5%)	1 (1.3%)	5 (2.6%)	.65
Vaso-occlusive crisis	57 (50.4%)	35 (46.1%)	92 (48.7%)	.55
Acute chest syndrome	9 (8.0%)	9 (11.8%)	18 (9.5%)	.37
Hospitalization	75 (65.2%)	40 (52.6%)	115 (60.2%)	.08
Maternal mortality	2 (1.7%)	1 (1.3%)	3 (1.6%)	1

The change in treatment strategy was not associated with a marked difference in the incidence of VOCs (50.4% in 2005–2010 vs. 46.1% in 2011–2014; $P = .55$), ACS (8% in 2005–2010 vs. 11.8% in 2011–2014; $P = .37$), or hospitalizations (65.2% in 2005–2010 vs. 52.6% in 2011–2014; $P = .08$) (Table 1).

Obstetric complication rates were similar in the two periods, including those related to hypertensive disorders (including pregnancy-induced hypertension, pre-eclampsia, eclampsia, and HELLP syndrome: 8.8% in 2005–2010 vs. 16% in 2011–2014; $P = .14$), oligohydramnios (0% in 2005–2010 vs. 3.9% in 2011–2014; $P = .06$), first trimester or late abortion (2.7% in 2005–2010 vs. 1.3% in 2011–2014; $P = .65$), and IUFD (0.9% in 2005–2010 vs. 1.3% in 2011–2014; $P = 1$) (Table 2).

As expected, the transfusion rate decreased after our change in transfusion strategy. Moreover, the proportion of patients receiving more than two transfusions decreased significantly (from 65.2% in 2005–2010 to 35.5% in 2011–2014; $P = .00006$), which may have been related to nocturnal prophylactic home oxygen therapy (Table 1). This decrease was observed in all phenotype subgroups. Specifically, we found that the proportion of SC patients (a subtype of SCD that tends to worsen markedly during pregnancy) receiving more than two transfusions decreased significantly (from 63.6% in 2005–2010 to 23.5% in 2011–2014; $P = .02$); this decrease was not associated with an increase in the complication rate (see below). The same trend was observed in SS pregnancies, with 67.1% receiving more than two transfusions in 2005–2010 and 40.4% receiving more than two transfusions in 2011–2014 ($P = .004$).

The post-transfusion complication rate also differed following the major change in transfusion strategy and oxygen therapy use. We observed post-transfusion complications (de novo alloimmunization and DHTR) in 6.1% of the patients in 2005–2010 and in 1.3% of the patients in 2011–2014 ($P = .15$) (Table 1). Notably, we did not observe

TABLE 2 Maternal outcomes and delivery

Period Pregnancies	2005–2010 *n* = 115 (60.2%)	2011–2014 *n* = 76 (39.8%)	Total *n* = 191 (100%)	*P* -
Hypertensive disorders	10 (8.7%)	12 (15.8%)	22 (11.5%)	.14
Hypertensive disease	4 (3.5%)	6 (8%)	10 (5.3%)	.2
Pre-eclampsia	8 (7.1%)	11 (14.5%)	19 (10.1%)	.1
Eclampsia	0 (0%)	0 (0%)	0 (0%)	
HELLP syndrome	1 (0.9%)	0 (0%)	1 (0.5%)	1
Oligohydramnios	0 (0%)	3 (3.9%)	3 (1.6%)	.06
Spontaneous/late abortion	3 (2.6%)	1 (1.3%)	4 (2.1%)	.65
Intrauterine growth retardation	5 (4.5%)	3 (3.9%)	8 (4.3%)	1
Intrauterine fetal death	1 (0.9%)	1 (1.3%)	2 (1.1%)	1
Cesarean section	79 (72.5%)	49 (70%)	128 (71.5%)	.72
Induction	20 (18.7%)	22 (32.4%)	42 (24%)	.03
Successful induction	14 (12.2%)	11 (14.5%)	25 (13.1%)	.02

HELLP, hemolysis, elevated liver enzymes, and low platelet count.

TABLE 3 Fetal outcomes, including prematurity

Periods Pregnancies	2005–2010 *n* = 115 (60.2%)	2011–2014 *n* = 76 (39.8%)	Total *n* = 191 (100%)	*P* -
Birth weight, g (range)	2930 (1350–4040)	2920 (525–4095)	2920 (525–4095)	.54
Term of birth, WA (range)	38 (32–41)	37 (26–41)	38 (26–41)	.19
Below the 10th percentile	8 (7%)	7 (9.2%)	15 (7.9%)	.57
Prematurity				
Less than 34 WA	9 (7.8%)	5 (6.6%)	14 (7.3%)	.75
Less than 37 WA	28 (24.3%)	23 (30.3%)	51 (26.7%)	.37
Apgar score below 10	23 (24.7%)	22 (33.3%)	45 (28.3%)	.24
Hospitalization in the neonatal intensive care unit	18 (19.6%)	17 (26.2%)	35 (22.3%)	.33
Perinatal mortality	1 (0.9%)	3 (3.9%)	4 (2.1%)	.30

WA, weeks of amenorrhea.

any *de novo* alloimmunizations in 2011–2014, and the only DHTR was observed in a woman with a previous reaction and a very high risk of recurrence.

The two study periods did not differ significantly in terms of the frequency of IUGR (4.5% vs. 3.9% in 2005–2010 and 2011–2014, respectively; $P = 1$), newborns below the 10th percentile (7% vs. 9.2%, respectively; $P = .57$), preterm delivery (24.3% vs. 30.7%, respectively; $P = .37$), a 5-minute Apgar score below 10 (24.7% vs. 33.3%, respectively; $P = .24$), or hospitalization in the neonatal intensive care unit (19.6% vs. 26.2%, respectively; $P = .33$) (Table 3). The overall mean gestational age was 38 WA (38 WA in 2005–2010 and 37 WA in 2011–2014; $P = .19$).

The maternal mortality rate (1.7% in 2005–2010 vs. 1.3% in 2011–2014; $P = 1$) and the perinatal mortality rate (0.9% in 2005–2010 vs. 3.9% in 2011–2014; $P = .30$) were similar in the two periods (Tables 1 and 3). In two cases, maternal death was related to a DHTR (a maternal-fetal death in an Hb SS woman at 25 WA, and a postpartum death in an Hb SS woman 17 d after delivery). Both women were known to have a very high risk of severe DHTRs and were transfused after a severe episode of ACS and a severe postpartum VOC, respectively. The third patient was a sudden maternal-fetal death in an Hb SC woman (found dead at home at 29 WA).

Overall, 184 of the 191 pregnancies (96%) resulted in a live birth, with 181 singleton deliveries (128 SS/Sβ0/SD women and 53 SC/Sβ+ women) and three twin deliveries (2 SS women and 1 SC woman). Three early miscarriages (at 10 WA for two cases and 12 WA for one case) and 1 late miscarriage (at 22 WA, twin pregnancy) were recorded. Furthermore, two cases of IUFD were related to two maternal deaths at 25 and 29 WA (Tables 1 and 2). One case of induced labor was complicated by rupture of the uterus and neonatal death after 7 d of life (unrelated to SCD).

No significant change in the type of delivery was observed as 70% of the patients underwent cesarean section. The type of delivery did not appear to vary as a function of the patient phenotype, the study period (2005–2010 or 2011–2014), or the mean gestational age. In some cases, cesarean section was performed because vaginal delivery was contraindicated (due to aneurysm, moya disease, or advanced retinopathy with a risk of retinal detachment). We noted that the frequency of induced labor (i.e., the vaginal administration of synthetic prostaglandins to dilate the cervix) was significantly greater in 2011–2014 than that in 2005–2010 and was associated with a 50% success rate (Table 2). The frequency of failed inductions did not vary significantly as a function of the phenotype or the mean gestational age. The induction procedure failed significantly more often in women under 18 years of age and in nulliparous women, although procedure failure did not appear to be related to SCD. Unfortunately, one case of scheduled, induced labor in a multiparous SC woman was complicated by unexpected rupture of the uterus (unrelated to SCD).

After adjustments for prognostic factors, the 2011–2014 period (corresponding to the cessation of routine prophylactic transfusions and the systematic recommendation of nocturnal home oxygen therapy) was not associated with a significantly higher frequency of VOCs and obstetric complications.

The only factors that were significantly associated with the occurrence of VOCs or ACS during pregnancy were patient age (OR [95% CI] = 0.90 [0.84-0.97]; $P = .008$) and a history of VOCs over the three years immediately preceding the pregnancy (OR [95% CI]=4.64 [1.98-10.9]; $P = .0004$). The factors associated with the occurrence of obstetric complications were age at the time of the pregnancy (OR [95% CI] = 1.11 [1.01-1.21]; $P = .03$) and nulliparity at the time of the pregnancy (OR [95% CI]=6.36 [2.10–19.3]; $P = .001$). Lastly, the only factors associated with the occurrence of complications during pregnancy (SCD and/or obstetric complications) were a history of VOCs over the three years immediately preceding the pregnancy (OR [95% CI] = 4.59 [1.92-11.01]; $P = .001$) and long-term therapy with HU or transfusion prior to the pregnancy studied (OR [95% CI] = 2.49 [1.09-5.68]; $P = .03$).

4 | DISCUSSION

Here, we reported the outcomes of 191 pregnancies in women with SCD between 2005 and 2014 who received care at two centers

(Necker Children's Hospital and Antoine Béclère Hospital). Our population of pregnant women had experienced various acute and/or severe chronic SCD-related complications, infectious or thromboembolic events, and obstetric complications.

Pregnant women have an elevated risk of SDB (including snoring and OSA). Interestingly, SDB is associated with adverse pregnancy outcomes, such as gestational hypertension.[27,39,40] Given that SDB and chronic hypoxemia, especially during the night,[16,17,20–22,28–31] may increase symptom intensity in pregnant women with SCD, and to counterbalance the restricted use of transfusion, we combined targeted transfusion with nocturnal prophylactic oxygen therapy at home from 2011 onward. This innovative treatment was based on a few previous observations and reports.[17] Nocturnal oxygen desaturation should be viewed as a surrogate marker for more severe disease. Importantly, pregnant Hb SS patients with baseline hypoxemia were found to have a 4-fold greater risk of severe complications or maternal death.[41]

The changes in our treatment strategy (including prophylactic oxygen therapy) were associated with a clear decrease in the transfusion rate, which was not related to a difference in maternal SCD events. We were very pleased to observe the absence of any de novo alloimmunizations or DHTRs during the 2011–2014 period. The only case of DHTR involved a patient with a history of this type of event; however, the patient was experiencing a life-threatening ACS and therefore, despite the very high risk of relapse, transfusion was essential. Although prophylactic oxygen therapy was not expected to influence the pathophysiology of alloimmunization and DHTR, the significant decrease in the occurrence of these complications is correlated with the decrease in the transfusion burden, which is subsequently related to the overall frequency of SCD complications.

Unfortunately, the patients' compliance with prophylactic home oxygen therapy during pregnancy and overnight pulse oximetry (to detect nocturnal hypoxemia) before the introduction of this treatment were not assessed systematically, which prevented us from analyzing a putative improvement in oxygenation with prophylactic oxygen therapy in this subgroup of women.

Few complications were observed in the newborns (in terms of birth weight, Apgar score and blood pH at birth, and hospitalization in the neonatal intensive care unit). Meanwhile, the frequency of SCD-related obstetric complications during the 2011–2014 period did not differ from that observed during the 2005–2010 period.

Importantly, we did not observe any severe maternal-fetal adverse events related to prophylactic oxygen therapy. The patients' self-reported tolerance was excellent, which led us to offer this treatment systematically as of 2011.

No definitive conclusion can be drawn from this retrospective study of two concomitant changes in our treatment strategy (i.e., targeted transfusion and prophylactic oxygen therapy). The methodological limitation of retrospective studies was highlighted in a recent meta-analysis by Malinowski et al.[42] Considering this limitation, we have set up a prospective, multicenter, randomized clinical trial (RCT) of prophylactic oxygen therapy during SCD pregnancies (NCT02813850). In fact, we hypothesize that prophylactic oxygen therapy relieves the symptoms of SCD (particularly during pregnancy). Accordingly, we intend to determine whether an independent effect on treatment outcomes exists in this high-risk medical setting. The study will investigate whether prophylactic oxygen therapy will decrease (i) the transfusion requirement and (ii) the incidence of severe post-transfusion complications without increasing the incidence of VOCs or obstetric complications. If this endpoint is met, prophylactic oxygen therapy may be of major value, especially in regions with sub-optimal transfusion safety. All the pregnant women with SCD in this ongoing RCT will undergo oximetry measurements for two consecutive nights so that we can establish whether the results are significant in a hypoxic subgroup only.

The use of prophylactic home oxygen therapy in SCD appears to be promising as (i) our patients currently request this new treatment option (despite its constraints), (ii) the preliminary results in previous studies have been positive,[33,43] and (iii) a pilot study of morbidity prevention in SCD by overnight supplementary oxygen has recently been initiated.[44]

Our results are consistent with several previous reports, as confirmed by a recent meta-analysis[45] in which prophylactic transfusion did not have an impact on VOCs, maternal/fetal complications, or obstetric complications, such as pre-eclampsia, fetal growth restriction, and perinatal mortality. Another recent meta-analysis (by Malinowski et al.[42]), however, showed that prophylactic transfusion was associated with decreased frequencies of maternal mortality, perinatal mortality, pain events, and pulmonary complications. The meta-analysis highlighted the variety of prophylactic strategies reported in the literature, with different transfusion techniques (top-up transfusions, manual transfusions, and erythrocytapheresis exchange) initiated at different stages of pregnancy, thus complicating the meta-analysis of the data. Oteng-Ntim et al.[45] suggested that systematic prophylactic transfusion did not appear to affect the occurrence of pre-eclampsia and fetal growth restriction, possibly because some of the events that damage the placental barrier occur in the first trimester when prophylactic transfusion has usually not yet been initiated.[42]

Malinowski et al.'s[42] meta-analysis also emphasized the lack of primary data on transfusion risks related to alloimmunization and DHTRs; however, others have observed a number of severe transfusion-related complications and have therefore developed a more targeted transfusion strategy.[12,46] During the 2005–2010 period, the post-transfusion complication rate was 6.1% (with de novo alloimmunization in 2.6% of cases and DHTRs in 3.5% of cases). The fact that two of the three maternal deaths resulted from DHTRs prompted us to restrict our indications for transfusion and to adapt prophylactic oxygen therapy. This finding is consistent with the guidelines issued in 2015 by the French Reference Center for Major Sickle Cell Syndromes.[47]

The results of the present study also highlighted several risk factors, such as patient age, nulliparity, and a history of VOCs and long-term therapy, for pregnant women with SCD. Our forthcoming prospective multicenter RCT should also enable us to establish a severity score and therefore adapt the therapeutic strategy according to a patient's risk factors.

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SUPPORTING INFORMATION

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