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# Impact of pre-eclampsia on renal outcome in sickle cell disease patients

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## Summary

The long-term consequences of pre-eclampsia (PrE) for renal function have never been determined in patients with sickle cell disease (SCD). Between 2008 and 2015, we screened 306 pregnancies in women with SCD and identified 40 with PrE (13%). The control group consisted of 65 pregnant SCD patients without PrE. In multivariable analysis, PrE events were associated with an increase of 1 log of lactate dehydrogenase level (adjusted odds ratio, aOR = 3.83,  $P = 0.05$ ), a decrease of 10 g/l of haemoglobin levels (aOR = 2.48,  $P = 0.006$ ) and one or more vaso-occlusive crisis during pregnancy (aOR = 16.68,  $P = 0.002$ ). Estimated glomerular filtration rate (eGFR) was similar in the two groups at steady state but was significantly lower in the PrE group after one year of follow-up and at last follow-up (130 vs 148 ml/min/1.73 m<sup>2</sup>,  $P < 0.001$  and 120 vs 130 ml/min/1.73 m<sup>2</sup>,  $P < 0.001$ , respectively). In multivariable analysis, eGFR had returned to steady-state levels one year after pregnancy in patients without PrE but continued to decrease in patients with PrE ( $\beta = -18.15$  ml/min/1.73 m<sup>2</sup>,  $P < 0.001$ ). This decline was more marked at the end of follow-up ( $\beta = -31.15$  ml/min,  $P < 0.001$ ). In conclusion, PrE episodes are associated with a significant risk of subsequent renal function decline in SCD patients.

**Keywords:** sickle cell disease, pre-eclampsia, chronic kidney disease, sickle cell nephropathy, risk factors.

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## Introduction

Sickle cell disease (SCD), the commonest inherited haemoglobinopathy worldwide, is associated with a higher risk of early death, due to acute complications and/or severe chronic organ dysfunction.<sup>1,2</sup> In recent decades, increases in the life expectancy of SCD patients have been accompanied by increases in the frequency of chronic kidney disease (CKD), accounting for 6–18% of overall mortality in these patients.<sup>3–6</sup> The identification of risk factors for renal impairment and progressive decline of glomerular filtration rate (GFR) in SCD patients is important, to make it possible to initiate early protective renal therapy.<sup>3</sup> Two studies recently showed that the deterioration of renal function was faster in SCD patients with severe genotypes [homozygous (HbSS) and sickle- $\beta^0$ -thalassaemia (HbS $\beta^0$ )] than in those with mild genotypes, sickle cell trait or without SCD.<sup>7,8</sup> A close relationship has also been found between rapid GFR decline and the risk of death.<sup>9</sup> In the general population, pre-eclampsia (PrE), defined as new-onset hypertension and proteinuria after 20 weeks of pregnancy, is associated with a higher risk of CKD and end-stage kidney disease (ESKD).<sup>10,11</sup> In a single-centre case-control study, Ngo *et al.* showed that PrE was more frequent in SCD patients (9.4%) than in the control group (2.3%).<sup>12</sup> Recent improvements in the care of SCD patients have decreased perinatal complications and mortality, for both newborns and

mothers.<sup>13,14</sup> However, the long-term impact of PrE on renal function in SCD patients remains to be determined.

In this study, we retrospectively analyzed the clinical and biological characteristics of a cohort of 40 SCD patients with PrE and compared the data for these patients with those for 65 SCD patients with PrE-free pregnancies, to determine whether PrE affected the renal function of these patients and to identify associated risk factors of PrE.

## Materials and methods

### *Experimental design, population and setting*

Between January 1, 2008 and December 31, 2015, we used a computerized database to identify, retrospectively, all pregnant women with SCD receiving prenatal care and giving birth in two maternity units involved in the medical care of SCD patients (Centre Hospitalier Intercommunal de Créteil, and Hôpital Tenon, Paris, France). This study was conducted in accordance with the Declaration of Helsinki and was approved by our local ethics committee (2020-078; Institutional Review Board No 0011558). SCD patients were included regardless of genotype: homozygous sickle cell disease (HbSS), haemoglobin SC disease (HbSC) and sickle  $\beta^+$ -thalassaemia (HbS $\beta^+$ ).

Our exposure of interest was PrE, defined as an increase in systolic blood pressure to  $\geq 140$  mm Hg or in diastolic

pressure to  $\geq 90$  mm Hg on two separate occasions in a patient who was previously normotensive, together with a proteinuria  $\geq 30$  mg/mmol according to urine protein/creatinine ratio (UPCR), after 20 weeks of pregnancy, representing the PrE-SCD group.<sup>15</sup> The exposure was determined by diagnosis codes and verified by chart review. Criteria for severe and early-onset PrE are described in Data S1.

The control group consisted of all SCD patients without PrE (no PrE-SCD), matched with the PrE group for year of pregnancy, SCD genotype, age at the start of pregnancy ( $\pm$ one year) and maternity unit. Medical charts of the control group were also reviewed to ensure the absence of PrE. The exclusion criteria for both groups were incomplete medical files, chronic hypertension requiring antihypertensive therapy, CKD, defined as estimated GFR (eGFR) below 90 ml/min/1.73 m<sup>2</sup> or UPCR  $>30$  mg/mmol during the first trimester of pregnancy, diabetes mellitus before pregnancy and twin pregnancies.

### Outcomes

The primary outcome was the assessment of eGFR decline following pregnancy, with or without PrE event, in comparison to steady-state eGFR within one year before pregnancy.

'Steady state' was defined as a consultation  $\geq 1$  month after a vaso-occlusion crisis (VOC) and  $\geq 3$  months after blood transfusion. Blood creatinine level was assessed for each patient at steady state within one year before pregnancy, defining baseline creatinine. Blood creatinine was then assessed during the first trimester of pregnancy, during PrE events, at the time of delivery, one year after pregnancy and

at the last follow-up visit. UPCR was recorded at the same time points. We estimated GFR (eGFR) with the creatinine-based CKD Epidemiology Collaboration (CKD-EPI) equation.<sup>7,8,16,17</sup> Acute kidney injury (AKI) was defined according to the Kidney Disease Improving Global Outcome (KDIGO) criteria<sup>18</sup> and AKI events were assessed within 48 h of delivery. CKD was defined and staged according to the criteria proposed by the CKD Working Group of KDIGO.<sup>19</sup>

The secondary objective consisted of the identification of potential risk factors of PrE in this population.

### Patient's evaluation

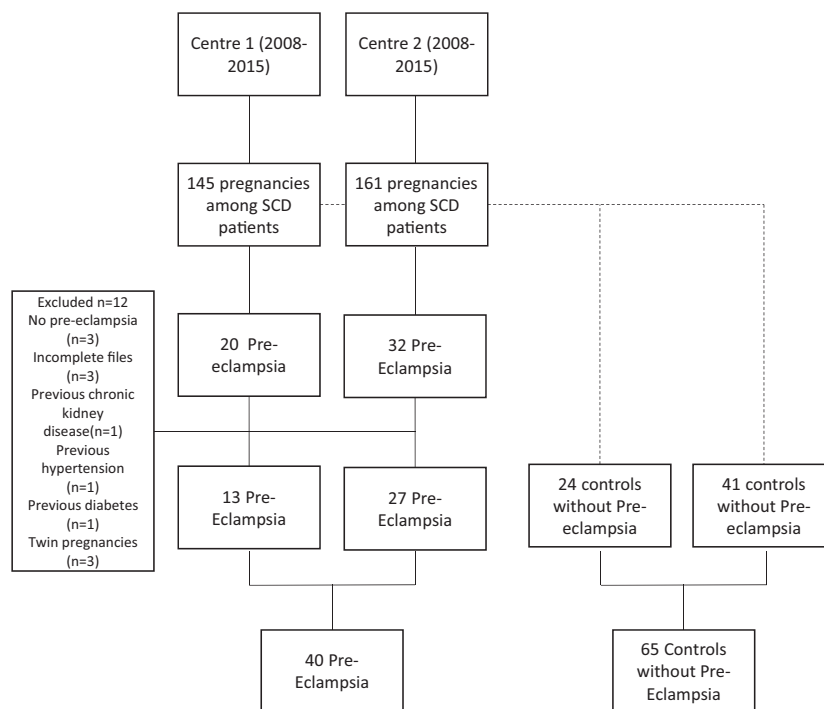
The clinical and biological data recorded for each patient are described in Data S1.

### Statistical analysis

Qualitative data were expressed as numbers and percentages  $n$  (%) and quantitative data were expressed as means ( $\pm$ SD) or medians (interquartile range) according to their distribution, with mixed logistic regression models used for comparison.

Regarding pre-eclampsia risk factors, associations were tested using mixed logistic regression models taking into account the matched nature of the data. Associations were estimated using crude and adjusted odds ratios (cORs and aORs, respectively) and their 95% confidence intervals.

Analyses of the change in eGFR over time were based on mixed linear regression models with random intercepts for repeated measurements. The first eGFR value, used as a reference value, was measured within one year before



**Fig 1.** Study flow chart. In all, 306 SCD pregnancies were screened between 2008 and 2015 at two French maternity units. In total, 40 SCD patients with PrE were enrolled in the study, and 65 SCD patients without PrE, matched for SCD genotype and age at pregnancy, were used as control group. SCD, sickle cell disease.

pregnancy, at steady state. Factors associated with the outcome were identified using univariate mixed linear regression models. The results were expressed as regression coefficients ( $\beta$ ) with 95% confidence intervals. We used multivariate modelling to determine whether PrE was associated with renal function in SCD patients, taking into account the variables associated with  $P < 0.20$  by univariate analysis and some variables known to be associated with eGFR decline (SCD genotype, steady-state haemoglobin (Hb), lactate dehydrogenase (LDH) levels and follow-up time). Pairwise analyses were done to assess confounding factors, and interactions were sought.

All tests were two-tailed and  $P < 0.05$  were considered statistically significant. Analyses were performed with STATA v15.0 (StataCorp, College Station, TX, USA).

## Results

### *Steady-state demographic, clinical and biological characteristics of SCD patients with or without pre-eclampsia*

Between January 2008 and December 2015, we identified 306 pregnant women with SCD followed at two French maternity units in the Ile-de-France area (Fig 1). PrE was reported in 40 (13%) of the cases retained (PrE-SCD group). The patients of the PrE-SCD group were matched with a control group of 65 pregnant women with SCD but without PrE (no PrE-SCD) (based on our selection criteria, the remaining 237 patients did not match the PrE-SCD group; Fig 1). The demographic, steady-state clinical and biological

characteristics of the two groups are summarized in Table I. There were 81 patients with the HbSS genotype (no PrE-SCD:  $n = 51$ ; PrE-SCD:  $n = 30$ ), 22 with the HbSC genotype (no PrE-SCD:  $n = 13$ ; PrE-SCD:  $n = 9$ ) and two with the HbS $\beta^+$  genotype (no PrE-SCD:  $n = 1$ ; PrE-SCD:  $n = 1$ ). Body mass index (BMI) was significantly higher in the PrE-SCD group than in the no PrE-SCD group [median BMI = 22 kg/m<sup>2</sup> (20–25) vs 20 kg/m<sup>2</sup> (19–22), respectively,  $P = 0.02$ ]. However, only two women in the PrE-SCD group had a BMI above 30 kg/m<sup>2</sup> versus one in the no PrE-SCD group. At steady state, the PrE-SCD patients had significantly lower levels of Hb [81.9 g/l ( $\pm 11.7$ ) vs 89.1 g/l ( $\pm 12.1$ ),  $P = 0.005$ ] and significantly higher levels of LDH [536 iu/l (332–710) vs 359 iu/l (310–430),  $P = 0.002$ ] than the no PrE-SCD patients.

### *Maternal and neonatal characteristics*

Maternal and neonatal characteristics during pregnancy are shown in Table II. Twenty-two (55%) patients with PrE and 34 (52.3%) in the no PrE-SCD group received prophylactic exchange transfusions of red blood cells ( $P = 0.8$ ). VOC requiring hospitalization was more frequent in the PrE-SCD than in the no PrE-SCD group [31 (77.5%) vs 31 (47.7%),  $P = 0.003$ ]. Gestational age at delivery was significantly lower in the PrE-SCD group than in the no PrE-SCD group [34.2 weeks ( $\pm 2.2$ ) vs 36.8 weeks ( $\pm 2.1$ ),  $P < 0.001$ ], due to PrE and/or abnormal fetal heart rate, which was more frequent in the PrE-SCD group [11 (27.5%) vs 5 (7.7%) in the no PrE-SCD group,  $P = 0.01$ ]. More deliveries were performed by caesarean section in the

**Table I.** Steady-state demographic, clinical and biological characteristics of sickle cell disease patients with and without pre-eclampsia.

Characteristics	Total	No pre-eclampsia	Pre-eclampsia	<i>P</i> value
<i>n</i>	105	65	40	–
SCD genotype (SS/SC/S $\beta^+$ ), <i>n</i> (%)				
SS	81 (77.1)	51 (78.5)	30 (75.0)	0.9
SC	22 (21.0)	13 (20.0)	9 (22.5)	
S $\beta^+$	2 (1.9)	1 (1.5)	1 (2.5)	
Ethnicity, <i>n</i> (%)				
Sub-Saharan African ancestry	97	59	38	>0.9
Caribbean ancestry	8	6	2	–
Age*, years, mean ( $\pm$ SD)	30.4 ( $\pm 4.80$ )	30.4 ( $\pm 4.80$ )	30.3 ( $\pm 4.85$ )	0.9
BMI**, kg/m <sup>2</sup> , median [IQR]	21 [19–23.3]	20 [19–22]	22 [20–25]	0.02
SBP*, mm Hg, mean ( $\pm$ SD)	102 ( $\pm 11$ )	102 ( $\pm 11$ )	103 ( $\pm 11$ )	0.6
DBP*, mm Hg, mean ( $\pm$ SD)	60 ( $\pm 10$ )	59 ( $\pm 9$ )	60 ( $\pm 11$ )	0.6
eGFR**, [ml/min/1.73 m <sup>2</sup> , median [IQR]	146 [139–156]	146 [139–154]	146 [139–156]	0.7
Hemoglobin level**, g/l, mean ( $\pm$ SD)	86.3 ( $\pm 1.24$ )	89.1 ( $\pm 1.21$ )	81.9 ( $\pm 1.17$ )	0.005
Plasma lactate dehydrogenase level**, IU/l, median [IQR]	370 [312–599]	359 [310–430]	536 [332–710]	0.002
History of VOC <i>n</i> (%)				
<3 per year	52 (49.5)	31 (47.7)	21 (52.5)	0.6
>3 per year	53 (50.5)	34 (52.3)	19 (47.5)	
History of ACS, <i>n</i> (%)	47 (44.8)	30 (46.2)	17 (42.5)	0.7
Hydroxyurea treatment before the start of pregnancy, <i>n</i> (%)	31 (29.5)	17 (26.2)	14 (35)	0.3

PrE-SCD group than in the no PrE-SCD group [31 (77.5%) vs 30 (46%),  $P = 0.003$ ]. Newborn weight was lower in the PrE-SCD group than in the noPrE-SCD group (2 219 g  $\pm$  661 vs 2 612 g  $\pm$  596,  $P = .004$ ). No neonatal deaths occurred in either of the groups. Similarly, none of the women died (Table II).

### Description of pre-eclampsia events

PrE occurred at 32 ( $\pm$ 3) weeks of pregnancy and 19 of the 40 women with PrE (47.5%) had early-onset PrE (Table III). PrE was considered severe in 27 patients (67.5%) (Table III).

In multivariate analyses, variables associated with PrE events at steady state were an increase of 1 kg/m<sup>2</sup> of BMI [aOR = 1.38 (1.14–1.70),  $P = 0.02$ ], an increase of 1 log of LDH level [aOR = 3.83 (1.00–14.66),  $P = 0.05$ ], a decrease of 10 g/l of steady-state Hb levels [aOR = 2.48 (1.30–4.72),  $P = 0.006$ ] and  $\geq 1$  VOC episode requiring hospitalization [aOR = 16.68 (2.72–102.11),  $P = 0.002$ ]. For renal parameters (Table III), median blood creatinine level at PrE diagnosis was 6.1 (5.1–7.4) mg/l and median UPCR was 127.5 (77.5–240) mg/mmol. Within 48 h of delivery, eight (20%) of the patients in the PrE-SCD group displayed AKI (five AKI stage 1, two AKI stage 2 and one AKI stage 3). In the no PrE-SCD group, six (9%) AKI events occurred after delivery, including five AKI stage 1 and one AKI stage 2 event. The frequency of AKI did not differ significantly between the two groups ( $P = 0.14$ ).

### Renal outcome in SCD patients with and without pre-eclampsia

Median follow-up was 54 (37–67) months in the no PrE-SCD group and 59 (37–77) months in the PrE-SCD group. At steady state and during the first trimester of pregnancy, median eGFR was similar in the two groups [steady state: eGFR = 146 (139–156) ml/min/1.73 m<sup>2</sup> and 146 (139–154) ml/min/1.73 m<sup>2</sup> in the PrE-SCD and no PrE-SCD groups, respectively,  $P = 0.7$ ; first trimester: 150 (141–160) ml/min/1.73 m<sup>2</sup> in PrE-SCD patients vs 150 (142–156) ml/min/1.73 m<sup>2</sup> in noPrE-SCD patients,  $P = 0.6$ ; Table IV]. By contrast, eGFR was significantly lower at the time of delivery in the PrE-SCD group than in the no PrE-SCD group [eGFR = 137 (108–146) ml/min/1.73 m<sup>2</sup> vs 140 (130–151) ml/min/1.73 m<sup>2</sup>,  $P = 0.03$ ]. One year after pregnancy and at the end of follow-up, eGFR remained significantly lower in the PrE-SCD group one year after pregnancy: 130 (116–142) ml/min/1.73 m<sup>2</sup> in the PrE-SCD group vs 148 (143–155) ml/min/1.73 m<sup>2</sup> in the no PrE-SCD group,  $P < 0.001$  and at last follow-up evaluation: 120 (103–135) ml/min/1.73 m<sup>2</sup> in the PrE-SCD group vs 139 (131–147) ml/min/1.73 m<sup>2</sup> in the no PrE-SCD group,  $P < 0.001$  (Table IV).

UPCR was negative in both groups during the first trimester of pregnancy [UPCR 10 (1–13) vs 10 (1–16.5) mg/mmol in the PrE-SCD and no PrE-SCD groups, respectively,  $P = 0.8$ ] but was significantly higher in the PrE-SCD group,

Table II. Maternal and neonatal characteristics.

Characteristics	Total	No pre-eclampsia	Pre-eclampsia	<i>P</i> value
<i>n</i>	105	65	40	–
Gravidity, median (IQR)	2 (2–4)	2 (2–4)	2 (2–3)	0.09
Parity, median (IQR)	1 (0–1)	1 (0–1)	1 (0–1.5)	0.9
Antiplatelet agents during pregnancy, <i>n</i> (%)	17 (16.2)	9 (14)	8 (20)	0.4
Use of exchange blood transfusion protocol during pregnancy, <i>n</i> (%)	56 (53.3)	34 (52.3)	22 (55.0)	0.8
$\geq 1$ blood transfusion during pregnancy, <i>n</i> ( $\pm$ SD)	65 (61.9)	36 (55.4)	29 (72.5)	0.08
$\geq 1$ VOC requiring hospitalization, <i>n</i> (%)	62 (59.1)	31 (47.7)	31 (77.5)	0.003
ACS during pregnancy, <i>n</i> (%)	3 (3)	1 (1.5)	2 (5)	–
Gestational diabetes, <i>n</i> (%)	3 (2.8)	2 (3)	1 (2.5)	–
Gestational age at delivery, weeks, mean ( $\pm$ SD)	35.8 ( $\pm$ 2.5)	36.8 ( $\pm$ 2.1)	34.2 ( $\pm$ 2.2)	<0.001
<34 weeks, <i>n</i> (%)	22 (21)	5 (8)	17 (42.5)	
34–37 weeks, <i>n</i> (%)	34 (32)	16 (25)	18 (45)	
>37 weeks, <i>n</i> (%)	49 (47)	44 (67)	5 (12.5)	
Intrauterine fetal deaths, <i>n</i> (%)	2 (2)	1 (1.5)	1 (2)	–
Caesarean delivery, <i>n</i> (%)	62 (59.1)	30 (46)	31 (77.5)	0.003
Postpartum haemorrhage, <i>n</i> (%)	8 (7.6)	3 (4.6)	5 (12.5)	0.15
Pulmonary embolism, <i>n</i> (%)	1 (0.9)	0 (0)	1 (2.5)	–
Abnormal fetal heart rate, <i>n</i> (%)	16 (15.2)	5 (7.7)	11 (27.5)	0.01
Fetal growth restriction, <i>n</i> (%)	10 (9.5)	4 (6.2)	6 (15.0)	0.145
Weight at birth, grams, mean ( $\pm$ SD)	2 462 ( $\pm$ 647)	2 612 ( $\pm$ 596)	2 219 ( $\pm$ 661)	0.004
Apgar score at 5 min, median (IQR)	10 (10–10)	10 (10–10)	10 (10–10)	0.36
Newborn deaths, <i>n</i> (%)	0 (0)	0 (0)	0 (0)	–

Qualitative data are expressed as *n* (%), quantitative data as means ( $\pm$ SD) or medians (IQR), as appropriate. Univariate mixed logistic regression model is used for comparisons. ACS, acute chest syndrome; IQR, interquartile range; VOC, vaso-occlusive crisis.

one year after pregnancy [20 (0–30) mg/mmol vs 10 (9–20) mg/mmol,  $P = 0.015$ ] and at the last follow-up assessment [20 (10–40) mg/mmol vs 11 (10–20) mg/mmol,  $P = 0.04$ ; Table IV]. In univariate analysis, one year's increase in age at the time of pregnancy [ $\beta = -1.03$  (–1.65 to –0.41) ml/min/1.73 m<sup>2</sup>,  $P = 0.001$ ] and the occurrence of more than one VOC requiring hospitalization during pregnancy [ $\beta = -5.92$  (–12.21 to 0.37) ml/min/1.73 m<sup>2</sup>,  $P = 0.065$ ] were associated with eGFR decline whereas an increase of one week in the delivery gestation age [ $\beta = 2.18$  (1.01–3.36) ml/min/1.73 m<sup>2</sup>,  $P < 0.001$ ] was associated with eGFR increase. Figure 2 shows the eGFR decline in comparison to steady-state eGFR, in each group and adjusted for age at pregnancy, VOC requiring hospitalization, delivery gestation age and several well-known factors of eGFR decline

**Table III.** Clinical and biological characteristics of pre-eclamptic events.

Characteristics	
Gestational age at which pre-eclampsia occurred, weeks, mean ( $\pm$ SD)	32 ( $\pm$ 3)
Severe pre-eclampsia, <i>n</i> (%)	27 (67.5%)
BP $\geq$ 180/110	21 (52.5%)
Eclampsia, <i>n</i> (%)	1 (2.5%)
HELLP syndrome, <i>n</i> (%)	4 (10%)
Platelet count $<100 \times 10^9/l$	1 (2.5%)
Persistent epigastric pain	2 (5%)
Early-onset pre-eclampsia, <i>n</i> (%)	19 (47.5%)
SBP/DBP, mm Hg, mean ( $\pm$ SD)	156 ( $\pm$ 11)/92 ( $\pm$ 9)
Haemoglobin level during pre-eclampsia, g/l, mean ( $\pm$ SD)	87 ( $\pm$ 10)
Platelet count during pre-eclampsia, $\times 10^9/l$ , mean ( $\pm$ SD)	310 ( $\pm$ 123)
Maternal admission to the ICU, <i>n</i> (%)	15 (37.5%)
Maternal death, <i>n</i> (%)	0 (0%)
Serum creatinine level, mg/dl, median (IQR)	0.61 (0.51–0.74)
eGFR, ml/min/1.73 m <sup>2</sup> , median (IQR)	137 (106.5–145.8)
UPCR mg/mmol, median (IQR)	127.5 (77.5–240)
AKI KDIGO stage $\geq 1^*$ during pre-eclampsia, <i>n</i> (%)	8 (20%)
AKI KDIGO stage 1	5 (12.5%)
AKI KDIGO stage 2	2 (5%)
AKI KDIGO stage 3	1 (2.5%)

Qualitative data are expressed as *n* (%), quantitative data as means ( $\pm$ SD) or medians (IQR), as appropriate. AKI, acute kidney injury; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate according to the CKD-EPI equation; HELLP, haemolysis, elevated liver enzymes, low platelet count; ICU, intensive care unit; IQR, interquartile range; KDIGO, kidney disease improving global outcomes; SBP, systolic blood pressure; UPCR, urine protein/creatinine ratio.

\*Stage 1: increase in serum creatinine level  $\geq 1.5$  to 1.9 times baseline or absolute increase  $\geq 26.5$   $\mu$ mol/l. Stage 2: increase in serum creatinine level  $\geq 2$  to 2.9 times baseline. Stage 3: increase in serum creatinine level  $\geq 3$  times baseline or absolute increase  $\geq 356.3$   $\mu$ mol/l or initiation of renal replacement therapy. Conversion factors for units: serum creatinine in mg/dl to  $\mu$ mol/l,  $\times 88.4$ .

including steady-state Hb levels and LDH levels, SCD genotype and duration of follow-up time. In the PrE-SCD group, a significant decrease was observed between steady state and one year after pregnancy [ $\beta = -18.15$  (–23.79 to –12.51) ml/min/1.73 m<sup>2</sup>,  $P < 0.001$ ], or last follow-up assessment [ $\beta = -31.15$  (–36.79 to –25.51) ml/min/1.73 m<sup>2</sup>,  $P < 0.001$ ]. By contrast, in the no PrE-SCD group, no significant difference was observed between steady state and one year after pregnancy ( $P = 0.54$ ), whereas there was a significant change by the last follow-up visit [ $\beta = -7.91$  (–12.33 to –3.48) ml/min/1.73 m<sup>2</sup>,  $P < 0.001$ ]. However, at the last follow-up visit, the decrease in eGFR was larger in the PrE-SCD group than in the no PrE-SCD group ( $P < 0.001$ ).

At the end of follow-up, 23 (57.5%) patients met the criteria for CKD in the PrE-SCD group: 15 CKD stage 1, seven CKD stage 2 and one CKD stage 5. By contrast, six (9%) patients presented CKD in the no PrE-SCD group: five CKD stage 1 and one CKD stage 2 ( $P < 0.001$ ; Table IV).

## Discussion

In this study, we found that PrE affected 13% of all SCD pregnancies between 2008 and 2015 in two French maternity units. At steady state, lower Hb levels, higher LDH levels and VOC during pregnancy were independently associated with PrE events. Strikingly, eGFR decline was greater in PrE-SCD patients one year after pregnancy and at last follow-up, even after adjustment for confounding factors.

PrE, one of the main causes of maternal and neonatal morbidity, affects 3–5% of all pregnancies in Western countries.<sup>20,21</sup> In this study, PrE was found in 13% of all pregnancies in women with SCD seen at the two obstetric units of the French Adult Sickle-Cell Referral Center, in agreement with previous studies.<sup>12,22</sup> At steady state, PrE-SCD patients had higher levels of intravascular haemolysis, as demonstrated by their lower Hb and higher LDH levels. The products of haemolysis exert multiple toxic effects by acting as damage-associated molecular patterns, promoting nitric oxide scavenging and reactive oxygen species (ROS) production.<sup>23</sup> Together, these processes lead to endothelial cell injury which may affect placenta homeostasis.<sup>23,24</sup> Strikingly, VOC episodes during pregnancy were independently associated with PrE events. In SCD patients, the initiation, progression and resolution of VOC can be considered as typical features of ischemia-reperfusion injury.<sup>25,26</sup> We hypothesize that VOC may promote placenta ischemia, thereby increasing the risk of PrE.

The long-term renal function outcomes of women with SCD after a PrE episode have never been investigated. In the general population, PrE is known to be associated with an increase in the risk of CKD, with an almost fivefold increase in the risk of ESKD reported in a population of 570 433 women.<sup>10</sup> After a median of 54 months of follow-up, eGFR had decreased by 7.9 ml/min/1.73 m<sup>2</sup> in the no PrE-SCD group, representing an annual decline in eGFR of –1.76 ml/min/1.73 m<sup>2</sup>. These results are consistent with the findings

Table IV. Association of pre-eclamptic events with long-term renal outcomes.

Renal parameters <i>n</i>	Total	No pre-eclampsia	Pre-eclampsia	<i>P</i> value*
Follow-up, months, median (IQR)	57 (37–67)	54 (37–67)	59 (37–77)	0.24
eGFR [ml/min/1.73 m <sup>2</sup> , median (IQR)]				
Steady state	146 (139–156)	146 (139–154)	146 (139–156)	0.7
First trimester of pregnancy	150 (142–157)	150 (142–156)	150 (141–160)	0.6
At delivery	140 (122–149)	140 (130–151)	137 (108–146)	0.03
One year after pregnancy	144 (131–152)	148 (143–155)	130 (116–142)	<0.001
At last follow-up visit	135 (120–144)	139 (131–147)	120 (103–135)	<0.001
UPCR, mg/mmol, median (IQR)				
First trimester of pregnancy	10 (1–15)	10 (1–16.5)	10 (1–13)	0.8
One year after pregnancy	14 (10–25)	10 (9–20)	20 (10–30)	0.015
At last follow-up visit	17 (10–30)	11 (10–20)	20 (10–40)	0.04
CKD ≥ 1, <i>n</i> (%) at the end of follow-up	29 (27.6)	6 (9)	23 (57.5)	<0.001
CKD stages, <i>n</i> at the end of follow-up				
Stage 1	30	5	15	
Stage 2	8	1	7	
Stage 3	0	0	0	
Stage 4	0	0	0	
Stage 5	1	0	1	

Qualitative data are expressed as *n* (%), quantitative data as means ( $\pm$ SD) or medians (IQR), as appropriate. CKD is defined by abnormalities of kidney function or structure present for more than three months. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate according to the CKD-EPI equation; IQR, interquartile range; SD, standard deviation; UPCR, urine protein/creatinine ratio; stage 1: eGFR >90 ml/min/1.73 m<sup>2</sup> with markers of kidney damage (albuminuria, haematuria, electrolyte disturbances); stage 2: eGFR between 60 and 89 ml/min/1.73m<sup>2</sup>; stage 3: eGFR between 30 and 59 ml/min/1.73 m<sup>2</sup>; stage 4: eGFR between 15 and 29 ml/min/1.73 m<sup>2</sup>; stage 5: eGFR < 15 ml/min/1.73 m<sup>2</sup>.

\*Univariate mixed logistic regression.

of a recent study by Derebail *et al.* reporting an annual change in eGFR of  $-1.82$  ml/min/1.73 m<sup>2</sup> in a retrospective cohort of 331 SCD patients.<sup>7</sup> We found that eGFR was significantly lower and kidney function decline significantly greater in the PrE-SCD group than in the no PrE-SCD group, both one year after pregnancy and at the last follow-up visit. Our data strongly suggest that PrE events may have a deleterious effect on renal function in SCD patients and should be considered an additional specific risk factor for renal function impairment in women with SCD.

PrE-SCD patients had lower steady-state levels of Hb and higher levels of LDH, two parameters associated with faster eGFR decline in SCD patients. Moreover, chronic haemolysis is associated with the early stages of sickle cell nephropathy (SCN).<sup>27,28</sup> Likewise, the frequency of VOC during pregnancy was higher in the PrE-SCD group than in the no PrE-SCD group. Olaniran *et al.* found that a higher frequency of SCD crises was associated with faster eGFR decline.<sup>8</sup> Recent studies found that AKI during VOC episodes occur in approximately 5% and 17% in adults and children, respectively.<sup>29–31</sup> AKI episodes seem to be closely related to VOC severity<sup>29</sup> and might be a consequence of tubular injury.<sup>32,33</sup> The respective contributions of PrE and VOC during pregnancy to the AKI observed in eight patients in the PrE-SCD group remain to be determined. However, even after adjustment for steady-state Hb levels and VOC episodes during pregnancy,

the decline in eGFR remained greater in the patients with PrE.

Another strength of this study is the assessment of blood pressure and kidney function (eGFR and UPCR) at steady state, confirming an absence of hypertension and CKD before pregnancy. Indeed, these pathological conditions have risk factors in common and are frequent confounders in studies of on the impact of PrE on renal outcomes.<sup>34</sup> However, it remains a matter of debate whether PrE is a direct cause or a marker of CKD in these patients. Indeed, PrE may exacerbate subclinical kidney diseases present before pregnancy. This hypothesis is particularly important in SCD patients, as early stages of SCN are characterized by hyperfiltration, as frequently observed in our cohort.<sup>3</sup> Ethnicity may affect renal function outcome. However, 92% of the patients in our cohort were from sub-Saharan African ancestry without difference between the two groups. In this setting, recent studies have demonstrated that SCD individuals carrying apolipoprotein L1 (APOL1) risk alleles (in the homozygous or compound heterozygous state) have a higher risk of developing SCN.<sup>35–38</sup> Likewise, APOL-1 is expressed in the placenta, and a fetal APOL1 high-risk genotype has been shown to increase the risk of PrE. However, the presence of maternal high-risk APOL1 alleles was not found to be associated with a higher risk of PrE in this previous



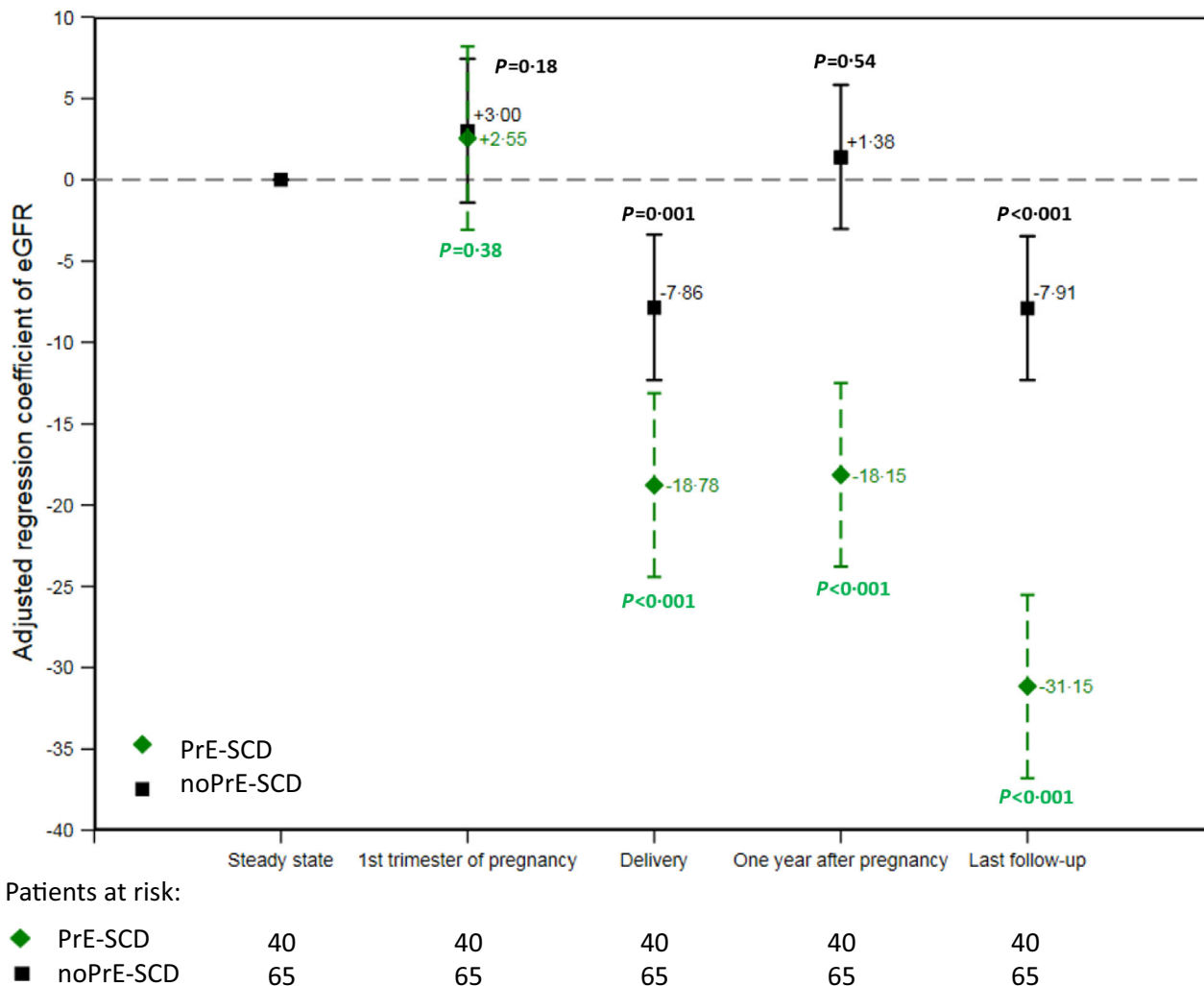


Fig 2. Change in estimated glomerular filtration rate (eGFR) in pregnant sickle cell disease patients with and without pre-eclampsia. Analysis of the change in eGFR at each time point (first trimester of pregnancy, delivery, one year after pregnancy and last follow-up visit) in comparison to steady-state eGFR, in both group, with mixed linear models for repeated measures. The results are expressed as regression coefficients ( $\beta$ ) with 95% confidence intervals. Confounding factors and interactions between group and time were assessed, and we used multivariate modelling to determine whether pre-eclampsia affected the renal function of the sickle cell disease (SCD) patients, with adjustment for age at pregnancy, VOC requiring hospitalization, delivery gestation age, steady-state haemoglobin (Hb) and LDH levels, SCD genotype and duration of follow-up time for steady-state Hb level, steady-state LDH levels, age at pregnancy, delivery gestational age, SCD genotype and duration of follow-up. Green lozenges represent PrE-SCD patients, and black squares, no PrE-SCD patients. PrE-SCD, sickle cell disease patients with pre-eclampsia during pregnancy; no PrE-SCD, sickle cell disease patients without pre-eclampsia during pregnancy; LDH, lactate dehydrogenase.

study.<sup>39</sup> Unfortunately, in our retrospective study, APOL1 genetic variants were not investigated and we cannot determine whether PrE-SCD patients exhibited more APOL1-G1/G2 risk variants compared to the noPrE-SCD group.

This study was subject to several limitations. The limited sample size of the PrE group somewhat weakens the strength of the comparison between PrE-SCD and no PrE-SCD patients. Only one patient from our cohort had ESKD at the end of follow-up. It therefore seems likely that a median follow-up of 57 months (for the entire cohort) is too short for an accurate assessment of the impact of PrE on the risk of ESKD. Similarly, although the decrease in eGFR in the PrE-SCD group was significant at the last follow-up visit,

clinicians would consider most of the individual eGFR values obtained to lie in the normal range. However, hyperfiltration is a typical feature of the early stages of SCN<sup>3</sup> and apparently normal eGFR values should be interpreted with caution in this particular population. Despite the use of a paired design and multivariate analysis, we cannot rule out the possibility that confounding factors also contributed to the rapid decline of eGFR in the PrE-SCD group. In this setting, Niss *et al.* recently demonstrated a close relationship between albuminuria and the deterioration of renal function in a population of adults with SCD.<sup>17</sup> Albuminuria was negative in both groups before pregnancy but was greater in the PrE-SCD group after pregnancy. However, because of the

retrospective design of our study, we did not manage to establish precisely which renal protective treatments were given to the patients after pregnancy.

In conclusion, our findings confirm the high prevalence of PrE in SCD patients and raises the hypothesis for haemolysis and VOC as independent risk factors for PrE events. It highlights the risk of a deterioration of renal function after a PrE episode in these patients. These findings provide strong support for the close monitoring of renal parameters in SCD patients experiencing PrE. Further studies are warranted to confirm the clinical value of this observation in long terms follow-up.

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## Author contributions

IB, MI-B, EB, F-CP, BH, PB, EL and VA designed the study. IB, EB, F-CP and VA designed the statistical analysis plan. IB collected the data. MI-B, AH, FL, AH, PG, TS, K-EK, DS, EF, PR, FG, EL, PB and BH collected the data, provided clinical and biological information and critically reviewed the manuscript. IB, MI-B, FCP, EM, EL, BH and VA analyzed the data. IB, EB, FC-P, EL and VA wrote the manuscript. Each author contributed important intellectual content during manuscript drafting. All authors read and approved the final version of the manuscript.

## Conflicts of interest

Dr Audard has received consulting fees from Addmedica outside the scope of the submitted work. All other authors have declared that no conflict of interest exists.

## Supporting Information

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

**Data S1.** Supplemental methods.

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