# Perinatal outcomes in women with sickle cell disease: a matched cohort study from London, UK

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# Summary

There are limited data on contemporary outcomes for women with sickle cell disease (SCD) in pregnancy. We conducted a single-site matched cohort study, comparing 131 pregnancies to women with SCD between 2007 and 2017 to a comparison group of 1310 pregnancies unaffected by SCD. Restricting our analysis to singleton pregnancies that reached 24 weeks of gestation, we used conditional Poisson regression to estimate adjusted risk ratios (aRRs) for perinatal outcomes. Infants born to mothers with SCD were more likely to be small for gestational age [aRR 1.69, 95% confidence interval (CI) 1.13–2.48], preterm (aRR 2.62, 95% CI 1.82–3.78) and require Neonatal Unit (NNU) admission (aRR 3.59, 95% CI 2.18-5.90). Pregnant women with SCD were at higher risk of pre-eclampsia/ eclampsia (aRR 3.53, 95% CI 2.00-6.24), more likely to receive induction of labour (aRR 2.50, 95% CI 1.82-1.76) and caesarean birth (aRR 1.44, 95% CI 1·18-1·76). In analysis stratified by genotype, the risk of adverse outcomes was highest in haemoglobin SS (HbSS) pregnancies (n = 80). There was no strong evidence that haemoglobin SC (HbSC) pregnancies (n = 46) were at higher risk of preterm birth, caesarean delivery, or NNU admission. Pre-eclampsia/eclampsia was more frequently observed in HbSC pregnancies. Despite improvements in the care of pregnant women with SCD, the increased risk of adverse perinatal outcomes remains.

Keywords: sickle cell disease, pregnancy, haemoglobinopathy.

# Introduction

Sickle cell disease (SCD) is the most common serious haemoglobinopathy and one of the most common single gene defects worldwide, affecting ~3 million individuals and >300 000 children are born with the condition annually. Over the last 40 years, dramatic improvements in the survival of individuals with SCD in high-income settings has led to the re-framing of SCD as a chronic condition with wideranging implications for health in adulthood.<sup>1</sup> Pregnancy in women with SCD is known to be associated with an increased risk of maternal, fetal and sickle complications.<sup>2,3</sup> Two recent meta-analyses pooled results from comparative studies focussing on the association between SCD and pregnancy; both reviews reported a fourfold increased risk of stillbirth in pregnancies complicated by SCD.<sup>4,5</sup> Additionally, these reviews reported that the incidence of preterm birth, pre-eclampsia and small for gestational age (SGA) were all

two- to four-times higher in pregnancies to women with SCD. However, the poor methodological quality of many previous studies has been noted, particularly the lack of information provided on the clinical management of SCD, the inability to stratify outcomes by SCD genotype, and the challenge in accounting for confounding by maternal characteristics.<sup>5</sup> A study conducted using the UK Obstetric Surveillance System (UKOSS) attempted to address some of these limitations, collecting data on 109 pregnancies in women with SCD between 2010 and 2011, and comparing the incidence of perinatal outcomes to national data on all pregnancies.<sup>2</sup> Although this study largely confirmed findings from previous reviews, the authors noted that a limitation of their study was the inability to use a more appropriate comparison group.

In the UK there are 100–200 births to women with SCD each year,<sup>2</sup> and although this forms a small proportion of the maternity population, these pregnancies are associated

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with high healthcare utilisation and costs. In 2011, the UK Royal College of Obstetricians and Gynaecologists (RCOG) published a guideline for the management of SCD in pregnancy.<sup>6</sup> This guideline, which has recently been updated,<sup>7</sup> provides the basis for best practice care in the UK and recommends multidisciplinary care through joint obstetric-sickle clinics, prophylactic folic acid to improve anaemia, penicillin to reduce risk of infection, and low-dose aspirin. The paucity of contemporary data on outcomes in pregnant women with SCD in the UK means it is unclear to what extent standardised clinical care over the last 10–15 years has ameliorated the increased risks associated with SCD in pregnancy.

We compiled a retrospective cohort of pregnancies in women with SCD receiving maternity care between 2007 and 2017 at a tertiary referral centre in London, UK. Drawing on a matched comparison group from the general maternity population, we aimed to assess perinatal outcomes of SCD in pregnancy in a contemporary setting with evidence-based optimal clinical management.

## **Patients and methods**

## Study design and population

This was a matched cohort study based on women receiving maternity care at Guy's and St Thomas' NHS Foundation Trust (GSTT) between 2007 and 2017. The GSST is a large tertiary referral hospital in London, UK, serving a diverse deprived inner-city population. The hospital has been running a specialist sickle-obstetric service since 2005, and the service leads have been closely involved in the development of the UK guidelines on SCD in pregnancy.<sup>6,7</sup> Over the study period, care for pregnant women with SCD at this centre was closely aligned to the 2011 UK RCOG guideline.<sup>6</sup> Briefly, standard management includes daily aspirin (75-150 mg) from pregnancy confirmation until 36 weeks of pregnancy, and prophylactic anticoagulation as per the RCOG guideline.<sup>6</sup> Most women receive blood transfusion ad hoc during pregnancy due to clinical indications (e.g. sickle cell crisis or severe anaemia) and prophylactic exchange is reserved for those who are already on exchange transfusion prior to pregnancy, multiple pregnancies, or those with previous poor obstetric or medical history. On confirmation of pregnancy, folic acid (5 mg daily) and prophylactic penicillin is initiated if the woman is not already taking these. Due to the increased risk of stillbirth, induction of labour (or elective caesarean if indicated) is recommended at 38-40 weeks. Non-steroidal anti-inflammatory drugs are the preferred method of pain relief in the postnatal period.

In this study, we included all singleton pregnancies to women with SCD who received antenatal care at the centre. For each SCD pregnancy, we randomly selected 10 singleton pregnancies unaffected by SCD but receiving care at the same hospital, matched on broad maternal ethnic category (Black, Asian, White, Mixed, Other) and delivery year. Pregnancies with known sickle cell trait (HbAS) were excluded as potential comparison pregnancies given the uncertainty regarding whether these pregnancies are also at increased risk of adverse perinatal outcome<sup>8</sup>; pregnancies to women with other (non-sickle) haemoglobinopathies were also excluded. Approximately 17% of pregnancies potentially eligible to be selected as comparison pregnancies had missing data on one or more covariate and/or outcomes, these were excluded from the selection process. Additionally, we excluded from both the SCD pregnancy cohort and comparison group any pregnancy that ended before 24 gestational weeks, and pregnancies which ended in termination at any gestational age.

## Data sources and outcomes

Relevant data were extracted from electronic maternity records, supplemented by manual abstraction from clinical records for SCD pregnancies. We recorded sociodemographic characteristics for all pregnancies: maternal age at delivery, ethnic group, parity, body mass index (BMI), smoking status at booking, and gestation at the initiation of antenatal care. Area deprivation was measured using the Index of Multiple Deprivation (IMD) for England quintiles, using 2010 scores for pregnancies during the period 2007 to 2011,<sup>9</sup> and IMD 2015 for pregnancies from 2012 onwards.<sup>9</sup> For SCD pregnancies we collected information on the SCD genotype.

Adverse perinatal outcomes of interest were maternal death, stillbirth (fetal death  $\geq$ 24 weeks and before birth), pre-eclampsia/eclampsia (raised blood pressure >140/ 90 mmHg with significant proteinuria), and preterm birth (<34 or <37 weeks completed gestation). Infant outcomes were SGA (<10<sup>th</sup> centile for gestation and sex-specific birthweight) and infant admission to the Neonatal Unit (NNU). Additionally, we collected information on induction of labour, caesarean delivery (emergency or elective), and postpartum haemorrhage (blood loss  $\geq$ 1000 ml).

#### Statistical analysis

We conducted descriptive analysis reporting outcomes by SCD status. To reflect the matched cohort design, we used conditional Poisson regression with robust variance estimators to estimate unadjusted and adjusted risk ratios (RRs) for the association between SCD and perinatal outcomes.<sup>10,11</sup> Our primary analysis used the combined SCD group, with additional analysis of pregnancies to women with the two main genotypes (HbSC and HbSS) separately. The reference group was always pregnancies unaffected by SCD. We adjusted for the following *a priori* covariates: maternal age, parity, BMI, and smoking status. Regression modelling was restricted to outcomes where there was a minimum of two events reported in both the SCD and comparison group. As a sensitivity analysis, all analyses were repeated using

generalised linear models fitted using a Poisson distribution with a log link function, ignoring the matched design and instead additionally adjusting for year of delivery. We used manual abstraction of data from medical records to minimise missing data, and we conducted a complete-case analysis. Analyses were performed using Stata version 16 (Stata Corp., College Station, TX, USA).

#### Ethical approval

This study received approval from the London School of Hygiene and Tropical Medicine Observational Research Ethics Committee (Ref. 15407-1).

### Results

We identified 131 eligible singleton pregnancies to women with SCD during the 10-year time period. Of these pregnancies, 80 (61·1%) were to women with HbSS genotype, 46 (35·1%) were to women with HbSC genotype, and five (3·8%) were to women with HbSB<sup>+</sup> genotype. Matching at a ratio of 10:1, we included 1310 singleton pregnancies to women without SCD who received care during the same period.

Maternal characteristics for these pregnancies are presented in Table I. All SCD pregnancies were to women of Black ethnicity, comparison pregnancies were matched using this broad ethnic grouping. Maternal age, parity, area-based deprivation category (IMD), and smoking status were all similarly distributed across the comparison and SCD pregnancies. There was a notable difference in BMI, with a higher proportion of maternal overweight/obesity in comparison pregnancies compared to SCD pregnancies (59·1% vs. 38·2%), with an even lower proportion of maternal overweight/obesity in HbSS pregnancies (22·5%). Women with SCD were more likely to initiate antenatal care early in pregnancy: nearly one quarter (22·1%) of SCD pregnancies involved an antenatal booking appointment before 10 weeks of pregnancy, compared to 15·4% of comparison pregnancies.

Among the SCD pregnancies there was one stillbirth (0.8%) and one maternal death (0.8%), both in pregnancies affected by HbSS (Table II). In the comparison cohort there were five stillbirths (0.4%) and no maternal deaths.

One in five (19.8%) newborns of women with SCD were SGA. This was reflected in an adjusted RR (aRR) of 1.69 [95% confidence interval (CI) 1.13–2.48] for all SCD pregnancies compared to unaffected pregnancies (Fig 1, Table SI). When stratifying by genotype, there was a significant increased risk of SGA for HbSC pregnancies, but not for HbSS pregnancies (Fig 2).

Preterm birth (<37 weeks) was higher in SCD pregnancies compared to comparison pregnancies (19·8% vs. 7·3%; aRR 2·62, 95% CI 1·82–3·78). When stratified by SCD genotype, the risk was highest for HbSS pregnancies (aRR for HbSS 2·93, 95% CI 1·80–4·79; aRR for HbSC 1·66, 95% CI 0·89– 3.08). In all, 6% of infants born to mothers without SCD required admission to the NNU compared to 18.3% of infants born to mothers with SCD (aRR 3.59, 95% CI 2.18–5.90). The risk of NNU admission in HbSC pregnancies was not significantly increased (aRR 2.08, 95% CI 0.77–5.64), but the risk for HbSS pregnancies remained elevated (aRR 5.48, 95% CI 2.90–10.38) (Fig 2).

The proportion of SCD pregnancies complicated by preeclampsia/eclampsia was higher than in unaffected pregnancies (13.0% vs. 3.5%), and there was evidence of an increased risk in multivariate analysis (aRR 3.53, 95% CI 2.00–2.64). When stratifying by SCD genotype, the risk of pre-eclampsia/eclampsia was significantly higher in both HbSC and HbSS pregnancies compared to non-SCD pregnancies (HbSC aRR 6.62, 95% CI 2.18–20.08; HbSS aRR 2.59, 95% CI 1.27–5.29).

Induction of labour was more common in SCD pregnancies compared to unaffected pregnancies (57·3% vs. 20·6%). In adjusted analysis, there was around a threefold increased risk of induction, with similar estimates for the combined SCD group and also when stratified by genotype (aRR for all SCD 2·90, 95% CI 2·40–3·50; aRR for HbSC 2·48, 95% CI 1·79–3·43; aRR for HbSS 3·13, 95% CI 2·45–4·00). Nearly half (45·0%) of pregnancies to women with SCD ended in a caesarean birth, with the equivalent figure for comparison pregnancies of 32·7%. In adjusted analysis the risk of caesarean birth was significantly higher when considering all SCD genotypes together (aRR 1·44, 95% CI 1·18–1·76) and HbSS pregnancies separately (aRR for HbSS 1·49, 95% CI 1·16–1·93). There was no strong evidence of an increased risk of postpartum haemorrhage (PPH) in SCD pregnancies.

Estimates from unmatched analyses were similar to estimates derived from the matched analysis (Table SII).

## Discussion

In the present matched cohort study comparing singleton pregnancies in women with SCD to unaffected pregnancies, we found a persistently higher risk of adverse perinatal outcomes associated with SCD. Infants born to mothers with SCD were more likely to be SGA, born preterm and require admission to NNU. Pregnant women with SCD were at higher risk of pre-eclampsia/eclampsia, and more likely to receive induction of labour, and caesarean birth. For most outcomes of interest, risk estimates were similar for both HbSC and HbSS pregnancies. However, there was some evidence that both NNU admission and preterm birth were more common in HbSS pregnancies compared to HbSC pregnancies, while HbSC pregnancies seemed to be at greater risk of preeclampsia/eclampsia compared to HbSS pregnancies.

### Interpretation

Two recent meta-analyses have attempted to quantify the excess risks associated with SCD in pregnancy.<sup>4,5</sup> Both of

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Characteristic	No SCD (comparison)	All SCD $(n = 131)$	HbSC $(n = 46)$	HbSS $(n = 80)$
	(n = 1310)			
	n (%)	n (%)	n (%)	n (%)
Age, years				
<20	45 (3.4)	3 (2.3)	1 (2.2)	2 (2.5)
20-24	181 (13.8)	20 (15.3)	3 (6.5)	16 (20.0)
25–29	376 (28.7)	37 (28.2)	12 (26.1)	25 (31.3)
30–34	376 (28.7)	40 (30.5)	19 (41.3)	19 (23.8)
35–39	238 (18.2)	24 (18.3)	9 (19.6)	14 (17.5)
≥40	94 (7.2)	7 (5.3)	2 (4.3)	4 (5.0)
BMI				
Underweight				
Normal	38 (2.9)	6 (4.6)	0 (0.0)	6 (7.5)
Overweight	498 (38.0)	75 (57.3)	17 (37.0)	56 (70.0)
Obese	416 (31.8)	34 (26.0)	21 (45.7)	12 (15.0)
Ethnicity				
Black	1310 (100.0)	131 (100.0)	46 (100.0)	80 (100.0)
Parity				
0	517 (39.5)	55 (42.0)	18 (39.1)	36 (45.0)
1-2	360 (27.5)	42 (32.1)	16 (34.8)	25 (31.3)
≥3	433 (33.1)	34 (26.0)	12 (26.1)	19 (23.8)
Smoker				
Yes	67 (5.1)	9 (6.9)	2 (4.3)	5 (6.3)
No	1243 (94.9)	122 (93.1)	44 (95.7)	75 (93.8)
IMD quintile				
1–2 (most deprived)	1150 (87.8)	110 (84.0)	37 (80.4)	68 (85.0)
3-5 (least deprived)	160 (12.2)	19 (14.5)	9 (19.6)	10 (12.5)
Missing	0 (0.0)	2 (1.5)	0 (0.0)	2 (2.5)
Gestation at booking				
<10 weeks	202 (15.4)	29 (22.1)	11 (23.9)	18 (22.5)
10-16 weeks	826 (63.1)	70 (53.4)	27 (58.7)	41 (51.3)
>16 weeks	282 (21.5)	23 (17.6)	7 (15.2)	15 (18.8)
Missing	0 (0.0)	9 (6.9)	1 (2.2)	6 (7.5)

BMI, body mass index; IMD, Index of Multiple Deprivation; SCD, sickle cell disease.

Table II. Perinatal	outcome by	sickle cell	disease	(SCD)	status.
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Perinatal outcome	No SCD (comparison) ( <i>n</i> = 1310) <i>n</i> (%)	All SCD ( <i>n</i> = 131) <i>n</i> (%)	HbSC ( <i>n</i> = 46) <i>n</i> (%)	HbSS ( <i>n</i> = 80) <i>n</i> (%)
Stillbirth	5 (0.4)	1 (0.8)	0 (0.0)	1 (1.3)
Small for gestational age	146 (11.1)	26 (19.8)	9 (19.6)	17 (21.3)
Preterm birth (<37 weeks)	96 (7.3)	26 (19.8)	6 (13.0)	19 (23.8)
Preterm birth (<34 weeks)	36 (2.7)	9 (6.9)	2 (4.3)	7 (8.8)
Neonatal Unit admission	72 (5.5)	24 (18.3)	5 (10.9)	19 (23.8)
Pre-eclampsia/eclampsia	46 (3.5)	17 (13.0)	7 (15.2)	10 (12.5)
Induction of labour	270 (20.6)	75 (57.3)	25 (54.3)	47 (58.8)
Caesarean birth	429 (32.7)	59 (45.0)	22 (47.8)	35 (43.8)
Postpartum haemorrhage	166 (12.7)	19 (14.5)	9 (19.6)	10 (12.5)
Maternal death	0 (0.0)	1 (0.8)	0 (0.0)	1 (1.3)

SCD, sickle cell disease.

these reviews reported a strongly increased risk of stillbirth and maternal mortality, ranging from a two- to fivefold increase in stillbirth, and an even higher risk of maternal mortality. We observed one stillbirth and one maternal death in our present cohort, both in HbSS pregnancies. Although the incidence of stillbirth and maternal death in the SCD

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(SCD) genotype and perinatal outcome.

cohort was higher than the comparison population, we did not have sufficient events to include these outcomes in adjusted analyses.

Poor fetal growth has long been established as a common outcome in pregnancies complicated by SCD12 and is likely attributable to abnormal placental development.<sup>13</sup> In our present study, SCD was associated with a 1.5-2-times higher risk of SGA, a slightly lower risk than previously reported.<sup>4,5,14</sup> Our present adjusted risk estimates for preterm birth suggest a twoto threefold increase in risk for SCD pregnancies, which is slightly higher than in previous studies.<sup>4,5,14</sup> Notably, the proportion of SCD pregnancies that ended in induction of labour was higher in our present cohort (57%) than in two recent cohorts from the UK and North America, which reported 39% and 22% respectively.<sup>2,14</sup> It is possible that the lower risk of SGA alongside a higher risk of preterm birth and induction of labour is explained by more pro-active and cautious management than in earlier studies, with a greater willingness to intervene and deliver earlier in pregnancy. Compared to infants born to mothers without SCD, we observed that infants born to mothers with SCD were more likely to be admitted for NNU care. When stratified by SCD genotype, the increased risk of NNU admission was only statistically significant for HbSS pregnancies. Although we were not able to identify any previous studies that reported this outcome, the increased risk of NNU admission is unsurprising given that infants born to women with SCD tend to be delivered at an earlier gestation. Among preterm pregnancies, the proportion involving a NNU admission was 54% and 44% for SCD pregnancies and non-SCD pregnancies respectively. However, we noted that among infants born at term, the risk of NNU admission was increased fourfold for pregnancies affected by SCD compared to non-SCD pregnancies (9.5% vs. 2.5%). This suggests that the increased risk of NNU admission among SCD pregnancies is not wholly attributable to the higher risk of preterm birth.

SCD is increasingly recognised as a risk factor for preeclampsia and eclampsia.<sup>4,5,14,15</sup> Standardised management for the SCD cohort reported here will have included lowdose aspirin antenatally.<sup>6</sup> Despite this, we observed that pregnancies complicated by SCD had a 3·5-times risk of preeclampsia/eclampsia. Interestingly, although HbSC is generally regarded as a less severe SCD genotype compared to HbSS, the risk of pre-eclampsia in HbSC pregnancies was considerably higher than in HbSS pregnancies (aRR 6·62 vs. 2·59). Mechanisms underlying the association between SCD and pre-eclampsia are still poorly understood,<sup>16</sup> although it has recently been postulated that SCD may amplify placental disease, with some suggestion that this may be irrespective of SCD genotype and pre-pregnancy health.<sup>13</sup>

Consistent with findings from a previous review,<sup>4</sup> we found no evidence to support an increase in the risk of PPH in pregnancies complicated by SCD.

### Implications

The two existing meta-analyses on this topic include pregnancies occurring as far back as the 1970s and 1980s. Based on pregnancies between 2007 and 2017, the present study provides updated evidence regarding outcomes associated with SCD in pregnancy. With the exception of preterm birth and induction of labour, our risk estimates were comparable or lower to those from previous studies. It is possible that this may in part reflect our choice of comparison group, while well-matched to our SCD pregnancies they are also drawn from a subgroup of pregnancies that may have a higher background risk of adverse perinatal outcome. The fact that our present risk estimates were comparable or lower than those from previous studies may reflect the improvements to clinical management in pregnancy and non-pregnancy care that have been made over the last 10-15 years. Early initiation of antenatal care alongside high-quality multidisciplinary care is the cornerstone of optimal management of pregnant women with SCD. It is notable that in our present SCD cohort, the mean gestation at booking was 13.5 weeks, considerably lower than the 17.3 weeks observed in a study of SCD pregnancies receiving antenatal care in the same setting between 2004 and 2008.17 Despite improvements in care, pregnancy in women with SCD clearly

remains high risk, particularly for the HbSS genotype, which is generally associated with a higher risk of adverse perinatal outcome.<sup>5,18</sup> Although HbSC genotype is often considered a more benign subtype, the risk of several adverse perinatal outcomes is also increased in HbSC pregnancies, suggesting that close surveillance and management is just as important for pregnant women with this genotype.<sup>2</sup> In addition to the risk of pregnancy-specific outcomes, sickle complications such as vaso-occlusive pain, infections and pulmonary complications are all observed more frequently in the pregnant SCD population compared to the non-pregnant SCD population.<sup>19,20</sup> Existing disease-modifying therapy for SCD is not currently recommended in pregnancy. Previous studies have suggested that between 30% and 70% of pregnant women with SCD require at least one clinically indicated blood transfusion during pregnancy,<sup>21,22</sup> and there is increasing interest in the potential use of chronic transfusion therapy in pregnancy. This has shown to be an effective disease-modifying therapy in the non-pregnant SCD population, used for primary and secondary stroke prevention and to reduce disease complications e.g. recurrent pain and recurrent acute chest syndrome.<sup>23</sup> However, there is insufficient evidence to support routine use of prophylactic exchange transfusion in pregnancy,<sup>24,25</sup> although a feasibility trial is currently ongoing.<sup>26</sup>

## Strength and limitations

The strengths of the present study include the fact that we included all singleton SCD pregnancies seen in the setting over the time period, and we were able to select a comparable group of pregnancies unaffected by SCD, matched on ethnic group and year of delivery. We were able to adjust for some key maternal characteristics, such as parity and maternal age. The study was conducted at a centre where care was consistently delivered according to best practice guideline, and within a universal and free at the point of access healthcare system.

SCD is a rare disease, and equally so are some of the relevant perinatal outcomes. We did not have sufficient power to examine the association between SCD and maternal or fetal mortality. We were able to stratify results according to the main two SCD genotypes, though small numbers impact on the precision of our estimates, particularly for the SC group which was smaller than the SS group. We should therefore be cautious about assuming that a lack of significance is synonymous with a lack of association.

Although we were able to extract data on a number of key perinatal outcomes, the limited data available for comparison pregnancies meant that we were unable to include several other outcomes of interest, such as maternal antenatal and postnatal hospital admissions, and neonatal mortality.

## Conclusion

Our present findings highlight that even with best practice contemporary management of SCD in pregnancy, the risk of adverse perinatal outcome is elevated. Although these risks are seen in both major SCD genotypes, there is evidence that pregnancies in women with HbSS are at highest risk of complications, although pregnancy in women with HbSC genotype is still associated with considerable risk. Alongside a continuing focus on preconceptual counselling and early initiation of high-quality multidisciplinary care in pregnancy for women with SCD, further research is needed regarding the pathology of adverse outcomes and appropriate interventions that could further lower the risk associated with SCD in pregnancy.

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# **Conflict of interest**

The authors have no financial conflicts of interest.

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#### Author contributions

Eugene Oteng-Ntim, Jo Howard and Susan E. Robinson set up the cohort of SCD pregnancies, and Inez von Rege, Sian Mitchell and Ruth Hadebe extracted the cohort data. Eugene Oteng-Ntim and Laura L. Oakley acquired the data on comparison pregnancies. Laura L. Oakley and Eugene Oteng-Ntim designed the present study, and Laura L. Oakley analysed the data. All authors were involved in the interpretation of data. Laura L. Oakley wrote the first draft of the paper, and all authors critically revised the paper. All authors approved the submitted version.

### **Supporting Information**

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

**Table SI.** Association between sickle cell disease (SCD) status and perinatal outcome.

**Table SII.** Association between sickle cell disease (SCD) status and perinatal outcome, comparing estimates from unmatched analysis (sensitivity analysis) and matched analysis (main analysis).

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