ORIGINAL RESEARCH

Pulmonary complications for women with sickle cell disease in pregnancy: systematic review and meta-analysis

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ABSTRACT

Background Sickle cell disease (SCD) is a multisystem disease characterised by vaso-occlusive crisis, chronic anaemia and a shorter lifespan. More patients with SCD are living till reproductive age and contemplating pregnancy. Pulmonary complications in pregnancy are significant causes of maternal morbidity and mortality but yet this has not been systematically quantified. A systematic review and meta-analysis were conducted to quantify the association between SCD and pulmonary complications in pregnancy.

Methods MEDLINE, EMBASE, Web of Science, Cochrane and Maternity and Infant Care databases were searched for publications between January 1998 and April 2019. Observational studies involving at least 30 participants were included. Random-effects models were used for statistical meta-analysis.

Findings Twenty-two studies were included in the systematic review and 18 in the quantitative analysis. The meta-analysis included 3964 pregnancies with SCD and 336 559 controls. Compared with women without SCD, pregnancies complicated by SCD were at increased risk of pulmonary thromboembolism (relative risk (RR) 7.74; 95% CI 4.65 to 12.89). The estimated prevalence of acute chest syndrome and pneumonia was 6.46% (95% CI 4.66% to 8.25%), with no significant difference between the HbSS and HbSC genotypes (RR 1.42; 95% CI 0.90 to 2.23).

Interpretation This meta-analysis highlighted a strong association between SCD and maternal pulmonary complications. Understanding the risks of and the factors associated with pulmonary complications would aid preconceptual counselling and optimal management of the condition in pregnancy, thereby reducing associated maternal morbidity and mortality.

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Key Messages

What is the key question?
► To what extent are pregnant women with sickle cell disease at increased risks of pulmonary complications?

What is the bottom line?
► Pregnancies with sickle cell disease are associated with an almost eightfold increased risk of pulmonary thromboembolism and a prevalence of 6.5% for acute chest syndrome and pneumonia.

Why read on?
► Understanding the risks of and the factors associated with pulmonary complications would aid preconceptual counselling and optimal management of the condition, thereby reducing associated morbidity and mortality.

INTRODUCTION

Sickle cell disease (SCD), as an autosomal recessive hemoglobinopathy, is a devastating multiorgan disease characterised by vaso-occlusive crises and chronic anaemia.[1] It is one of the most common genetic disorders globally with over 300 000 children born with the condition each year.[2] The life expectancy is reduced for people with SCD.[3] With the introduction of neonatal screening for SCD and the increased awareness of the importance of antibiotic prophylaxis and multidisciplinary management, more women are living till reproductive age and contemplating pregnancy.[4] In the UK, there are approximately 100–200 pregnancies in women with SCD per year.[5] Pregnancies complicated by SCD are associated with increased risk of adverse maternal and perinatal outcomes[6 7]

Individual studies have shown that pregnant women with SCD are at increased risk of pulmonary complications. In particular, pulmonary complications including acute chest syndrome (ACS), pneumonia, pulmonary thromboembolism (PTE) and pulmonary hypertension (PH) are significant causes of maternal morbidity and mortality.[8] However, the heterogeneity inherent with the disease expression of SCD and with the setting of these studies leads to uncertainty when estimating the associated risks.[9] The lack of comprehensive data on pulmonary complications for pregnant women with SCD has led to difficulties in preconceptual and antenatal counselling as well as clinical care pathways. The aim of this study is to systematically review and meta-analyse the risks of pulmonary complications in pregnancies complicated by SCD compared with pregnancies without SCD. In addition, we aim to evaluate whether the risk is greater for HbSS genotype compared with HbSC genotype, and to identify the proportion of maternal mortality associated with pulmonary complications.

METHODS

Search strategy

A systematic review and meta-analysis were performed according to the Meta-analysis of Observation Studies in Epidemiology group criteria and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[10] The following databases were searched for articles published between 20 January 1998 and 15 March 2019 for titles and abstracts related to our research question: MEDLINE via Ovid, EMBASE, Cochrane, Web of Science, Maternity and Infant Care. Abstracts and full-text articles were reviewed by two assessors (SI and MB) independently and results were compared. In addition, we cross-examined references from relevant original papers and reviewed articles to identify further relevant studies. This systematic review and meta-analysis were limited to English-language articles.

Study selection

Studies were included in the systematic review if they met the following criteria: the study design was observational; the exposure of interest was SCD in pregnancy; pulmonary complications were reported and a minimum of 30 pregnant women with SCD were included as smaller studies tend to be of variable quality and add very little to the findings. We excluded animal studies, conference abstracts and manuscripts related to sickle cell trait only.

Data extraction

Data extraction was carried out independently by the two assessors using a standard extraction form. Two assessors undertook the screening for papers, read full-texts and assessed the final selection of papers. In the case of disagreement, a third assessor was consulted. The following information from each study was extracted: authors; year of publication; study name; study design; country of study, study setting, number of participants, relevant outcomes on pulmonary complications including ACS, PTE, pneumonia, PH and maternal mortality secondary to pulmonary complications. We obtained the gross national income per capita for each study location from World Bank data.

Quality assessment

The Newcastle-Ottawa scale (NOS) was used to evaluate the quality of the papers.[11] The studies were evaluated with regard to three aspects: selection of the study groups, comparability of the groups and assessment of outcome, with a total of nine stars available. The studies were categorised as high (7–9), medium (4–6) or low grade (1–3) (online supplementary table S2).

Statistical analysis

Analyses were pregnancy based. The main measure of effect of maternal SCD on pulmonary complications during pregnancy was the unadjusted risk ratio, calculated from the given numbers of pregnancies and events. We undertook separate comparisons for women with HbSS and HbSC genotypes, as well as for pregnancies managed in high-income and low-income and middle-income settings, for the prevalence of ACS and pneumonia. Depending on the outcome under consideration, studies with no events in either arm were excluded. To assess the association of each pulmonary complication in pregnancy for women with SCD, random-effects models were used for statistical meta-analysis.[12] Heterogeneity of the studies was tested with the Breslow-Day test to measure inconsistency.[13] The level of heterogeneity was expressed as I^2. An I^2 score >50% was agreed to indicate high heterogeneity. Publication bias (due to the non-publication of small, non-significant studies) was not relevant in discussing prevalence study as significance tests were not used. For PTE, there were too few studies (n=2) for a formal test. Based on the results obtained from the funnel plots, we used random-effects model. We have used the continuity correction of a 0.5 when there were zero events. Stata V.15.1 was used for all statistical analyses.

RESULTS

A flow chart for identification of papers and subsequent evaluations is shown in figure 1. After the exclusion of ineligible papers, 22 papers were included for narrative review and 18 papers for quantitative analysis.

Study characteristics

The characteristics of the studies included in the systematic review and meta-analysis are outlined in online supplementary table S1.[14–35]

Of the 22 studies included in the systematic review, 4 studies were prospective cohort studies, 17 retrospective and 1 was both retrospective and prospective. Thirteen studies were from high-income countries (HIC) and nine were from low-income or medium-income countries (LMIC). Seven studies were considered to be of high quality and 15 of medium quality (online supplementary table S2). The meta-analysis included 3964 pregnancies with SCD and 336 559 pregnancies without SCD. Of the 22 studies, 11 used pregnant women with normal haemoglobin (HbAA) as a control group and 11 studies did not include a control group.

Prevalence of ACS and pneumonia in pregnant women with SCD

Eighteen studies evaluated outcomes of ACS and pneumonia. Regarding the clinical case definition of ACS, four studies[20 26 30 32] applied the standard of new pulmonary signs/symptoms accompanied by new pulmonary infiltrates on chest X-ray[36]; the other 10 studies did not state a formal case definition. We have taken this into account when assessing the quality of the studies using the NOS scale.[11] In view of the difficulty in distinguishing ACS from pneumonia clinically, we have chosen to evaluate ACS/pneumonia as a combined outcome when assessing its prevalence.

There was a strong evidence of heterogeneity (I^2=89.29%). The funnel plot (figure 2) showed that the larger studies tended to have much smaller event rates. Studies with event rates under 5% were typically larger (mean size 383, compared with 90), but identified fewer cases (mean 7.35, compared with 13.8). Because of this, some of the largest studies (Rajab *et al*[27] and Al Kahtani *et al*[17]) had bigger SE and less accurate estimates (on the log scale) than smaller studies such as by Silvia-Pinto *et al*,[31] Soh *et al*[32] and Al-Farsi *et al*.[14]

The meta-analysis and forest plot therefore considered event rates by sample size (figure 3). The smaller studies (n<100 and n=100–150) gave estimates of 15.04% (95% CI 8.18 to 21.91) and 10.07% (95% CI 3.48 to 16.66). For the six largest studies the estimate was 2.82% (95% CI 1.33 to 4.31). The composite estimate was 6.46% (95% CI 4.66 to 8.25). Even after allowing for sample size, there was considerable heterogeneity which we were unable to explain. There was no significant difference in the prevalence of ACS/pneumonia between the HbSS and HbSC genotypes (relative risk (RR) 1.42; 95% CI 0.90 to 2.23) (figure 4). LMIC (countries with a gross national income per capita of US$30 000 or less) had a higher prevalence of ACS/

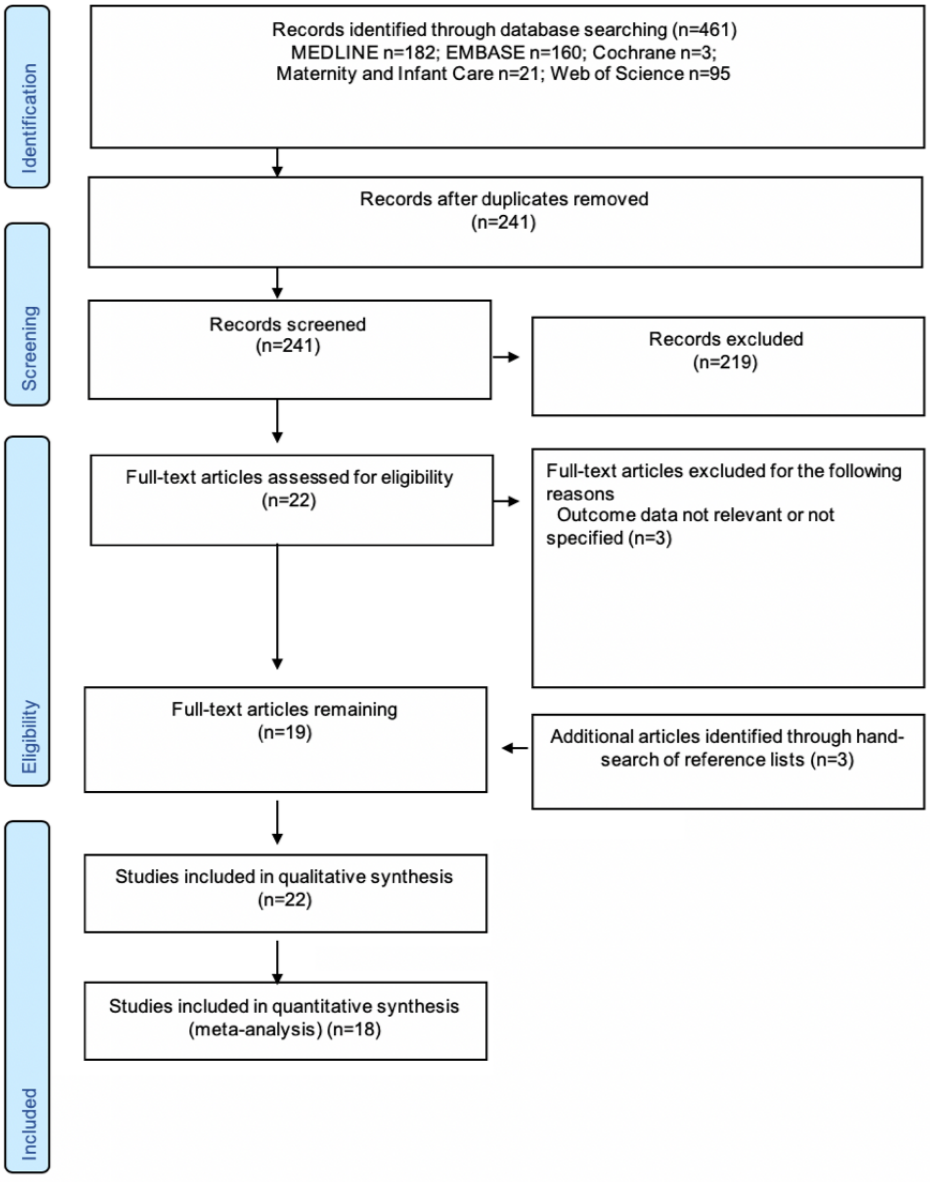

Figure 1 Flow chart of study selection.

pneumonia (13.9%) compared with HIC (4.9%) (p=0.03) (figure 5).

Pulmonary thromboembolism

Of the six studies that reported outcome on PTE, only two included a control group of women with HbAA. The estimated prevalence of PTE in women with SCD in pregnancy was 105/10 000 (95% CI 65 to 170) and the estimated prevalence of PTE in women without SCD in pregnancy was 13.8/10 000 (95% CI 12.5 to 15.1). There was nearly an eightfold increased risk of PTE in women with SCD (RR 7.74; 95% CI 4.65 to 12.89) (figure 6).

Pulmonary hypertension

There was only one study that looked at PH in pregnancy for women with SCD.[33] This study reported a statistically significant increase in the occurrence of PH in pregnancies with SCD compared with pregnancies without SCD, with an OR of 6.3 (95% CI 2.1 to 18.8).[33] An additional study investigated women with a tricuspid regurgitant velocity (TRV) >2.5 m/s, however, it was acknowledged that TRV >2.5 m/s has a high false positive rate and does not reliably predict PH.[32]

Maternal deaths due to pulmonary complications

Six studies reported maternal deaths and overall 88% of the maternal deaths reported were secondary to pulmonary complications.[16 18 20 27 29 31] Four studies provided no evidence of any autopsies being done. The studies from Ghana[18] and Jamaica[29] stated some autopsy-derived pulmonary pathologies (table 1). The true pathological causes of death in the other reported instances were unknown (see online supplementary table S3 for a series with systematic autopsy pathology).

DISCUSSION

This systematic review and meta-analysis identified a strong association between pregnancies with SCD and pulmonary complications, including ACS/pneumonia and PTE. In addition, pulmonary complications contributed substantially to maternal mortality in women with SCD. We believe this meta-analysis is the first review to provide pooled relative risks for pulmonary

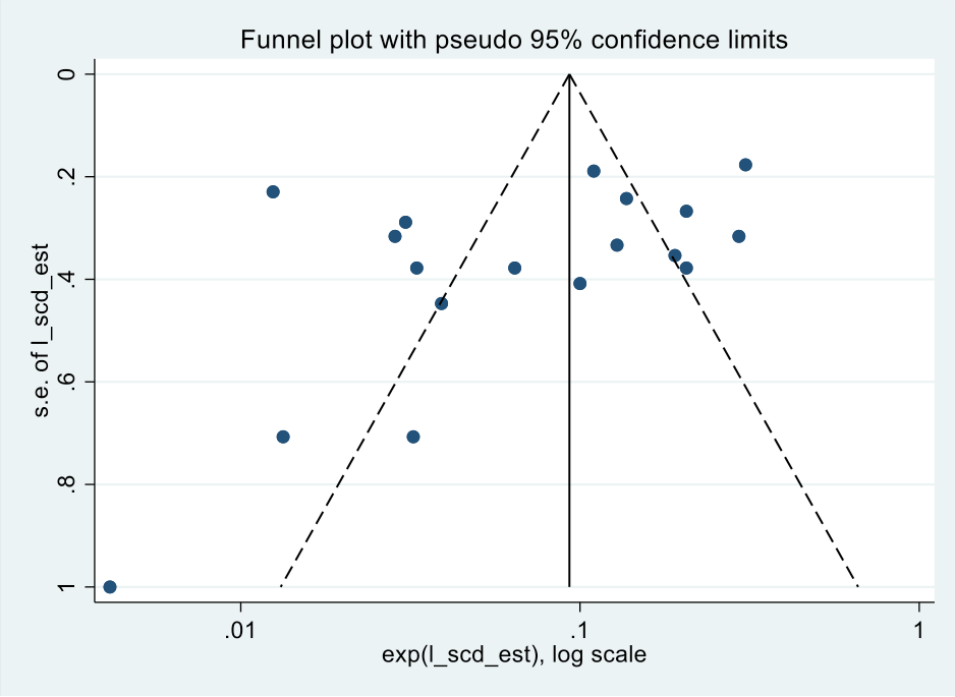

Figure 2 Funnel plot of studies investigating the prevalence of acute chest syndrome/pneumonia in pregnant women with sickle cell disease, by sample size.

complications in women with SCD in pregnancy, and to present prevalence estimates of ACS/pneumonia according to genotype. This review was strengthened by a comprehensive search strategy and a large pooled sample size of almost 4000 pregnancies with SCD. It remains a limitation that a small number of women contributed more than one pregnancy to an individual

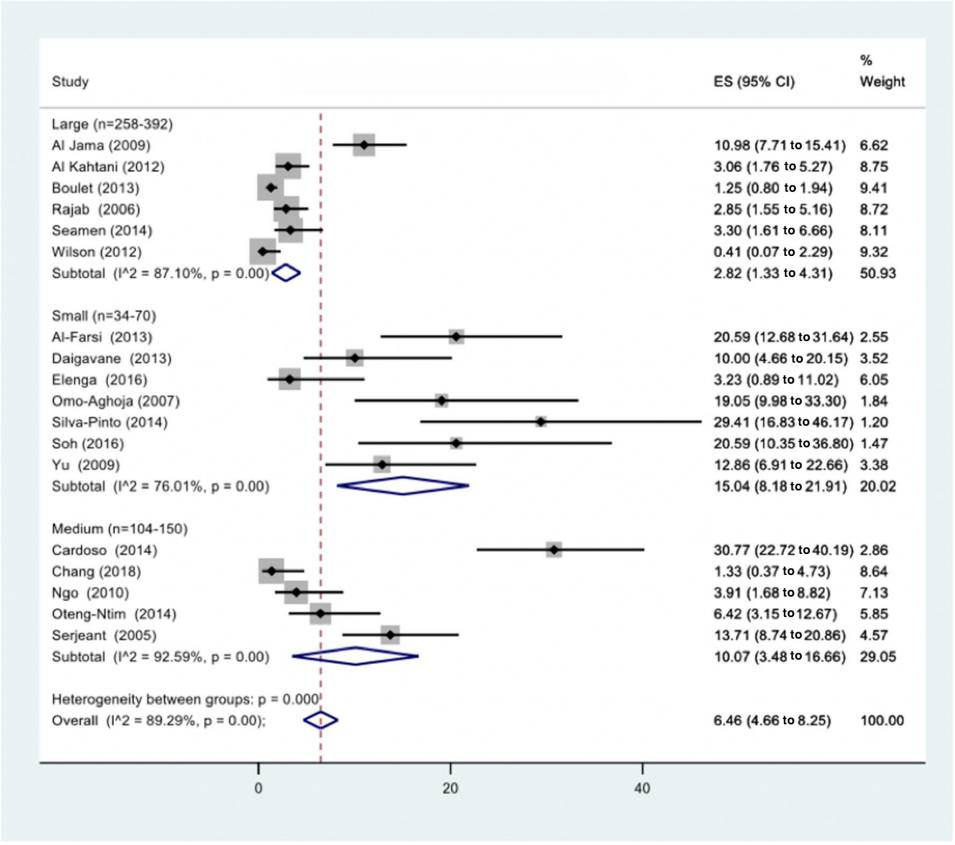

Figure 3 Forest plot of studies investigating the prevalence of acute chest syndrome/pneumonia in pregnant women with sickle cell disease, by sample size.

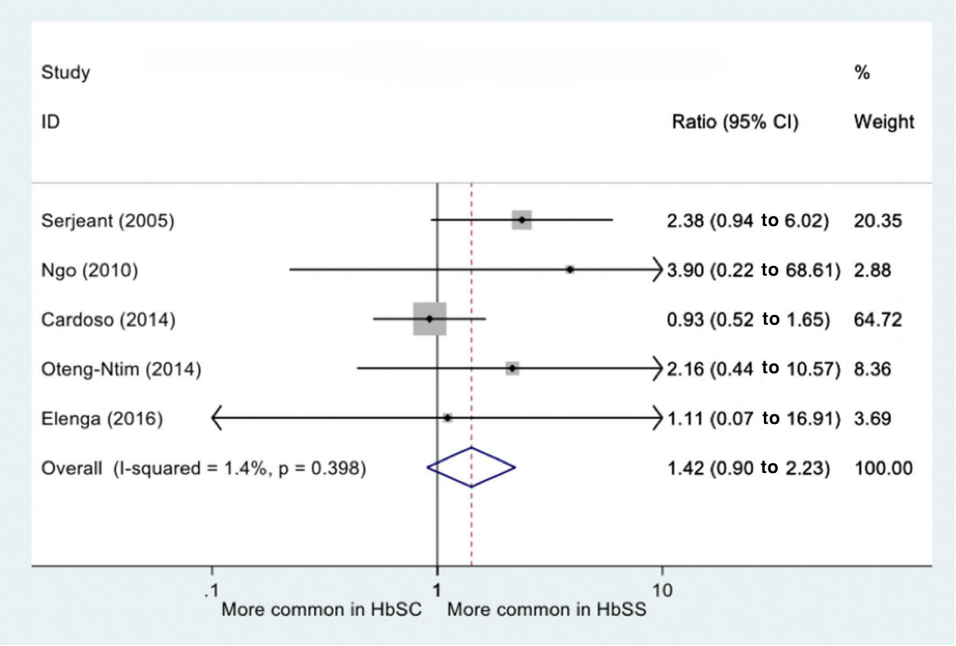

Figure 4 Forest plot of studies comparing the prevalence of acute chest syndrome/pneumonia in HbSS and HbSC genotype.

study. Without individual patient data, it was not possible to take this into account. In addition, comparisons between groups of women (eg, ACS/pneumonia prevalence in women with HbSS and HbSC) were not adjusted for possible confounding factors such as maternal age and parity as individual patient data were not available.

The meta-analysis indicated that the prevalence of ACS/pneumonia is 6.46% for women with SCD during pregnancy. However, heterogeneity between studies was large, and the findings should be interpreted with caution. We acknowledge that ACS is a separate clinical entity to pneumonia with a different pathophysiology.[36] However, clinically the differentiation of

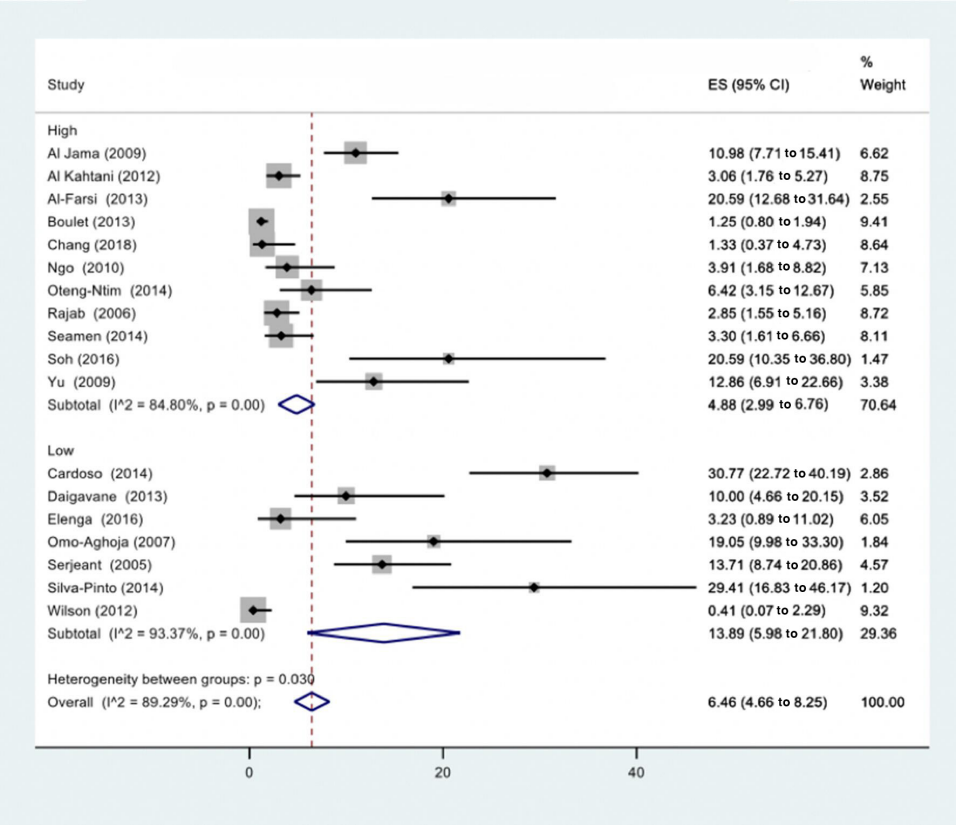

Figure 5 Forest plot of studies investigating the prevalence of acute chest syndrome/pneumonia in high-income setting vs a low-income and middle-income setting.

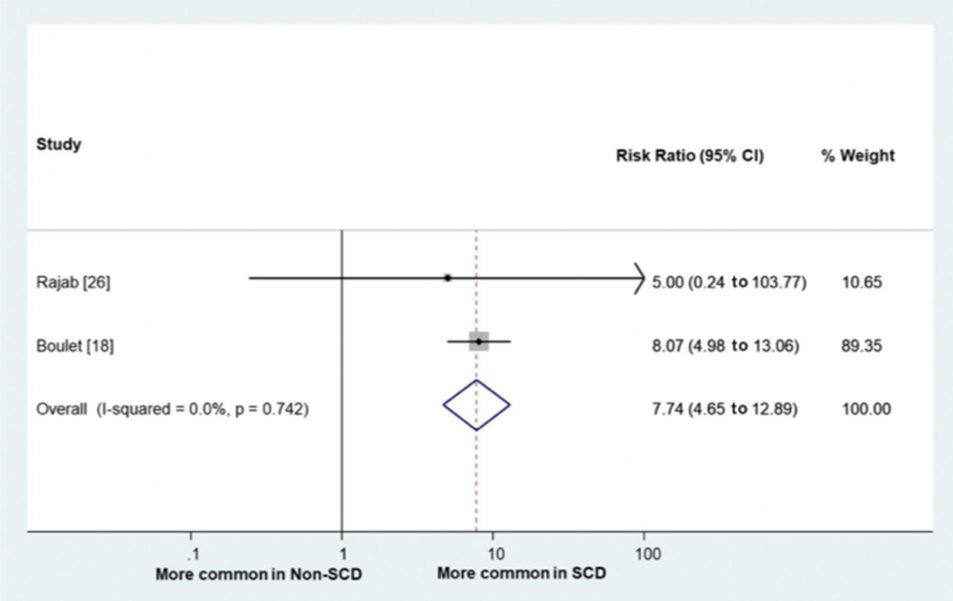

Figure 6 Forest plot of studies investigating the association of sickle cell disease (SCD) with pulmonary thromboembolism.

ACS from other diagnoses, especially pneumonia, can often be challenging, and at times artificial. Therefore, we have reported ACS/pneumonia as a single outcome. Two studies observed that ACS occurred most frequently in the third trimester and early postpartum period,[30 35] a finding that was also highlighted by a more recent study by Asare *et al*.[37] However, most included studies did not report on the timing of ACS therefore we were unable to stratify prevalence estimates by trimester.

ACS/pneumonia prevalence was higher in LMIC compared with HIC. This finding was consistent with two recent systematic reviews and meta-analyses which indicated significantly higher maternal mortality for pregnancies with SCD in LMIC compared with HIC.[6 7] These findings are likely to reflect variations in treatment pathways and standards of care across settings. One study from an HIC was unique in reporting a management pathway involving prophylactic exchange transfusions. This may have altered their reported outcomes on pulmonary complications,[24] although the evidence regarding any beneficial impact of prophylactic transfusion is inconsistent.[38 39] There is evidence that maternal mortality due to pulmonary complications can be reduced with a multidisciplinary approach. In a low-resource setting in sub-Saharan Africa, implementing a multidisciplinary care strategy with a joint obstetric haematology clinic reduced maternal mortality by 89% in a pre-intervention and postintervention study, and a comparable mortality rates to women without SCD can be achieved.[40 41] In settings in which multidisciplinary care for this population is already well established, further research is needed to identify areas of improvement.

There was no statistically significant difference in the prevalence of ACS/pneumonia for women with HbSS genotype compared with HbSC genotype. This is in contrast to the general perception that HbSC is overall a clinically more benign phenotype than HbSS with regard to maternal and fetal complications.[7] The incidence of ACS in the general adult SCD population is known to be lower for adults with HbSC genotype (5.2 per 100 patient-years) when compared with HbSS genotype (12.8 per 100 patient-years).[42] It may be that pregnancy is a specific process which heightens risk for women with HbSC. However, it should be noted that a small pooled sample size was used for the genotype-specific meta-analysis. In addition, some cases of HbSC might not be correctly depicted as HbSC. We note that two of the five studies included did not report on the method they used to distinguish the genotypes.

The high prevalence of ACS/pneumonia in women with SCD may relate to the increased susceptibility to infections during pregnancy. Early recognition and prompt management of respiratory infections may reduce painful crises[15] and ACS.[8 43] The eightfold increased risk of PTE in pregnancy in women with SCD confirms the need for appropriate thromboprophylaxis, especially for women with other risk factors (RCOG guideline 2015).[44]

Women with SCD, particularly those with PH, should get preconceptual counselling about the risks associated with pregnancy. Earlier studies identified a maternal mortality of 56% in pregnant women with secondary vascular PH[45] and women with PH are often advised against pregnancy.[46] A key public health issue to highlight is provision of appropriate contraceptive advice for women with SCD of reproductive age. Progestogens and intrauterine devices are effective and safe methods. There are some concerns with the use of combined contraceptive pill

Table 1 Maternal deaths due to pulmonary complications of sickle cell disease

Study	Maternal deaths due to pulmonary complications	Total maternal deaths
Al Julfairi *et al*[16]	Two due to PE, 1 due to ACS	4
Asare *et al*[18]	► 8/44 deaths with autopsy report due to PE ► 33/44 deaths due to a clinical diagnosis of ACS*	44
Resende Cardoso *et al*[20]	4	5
Rajab *et al*[27]	3	4
Serjeant *et al*[29]	One autopsy-confirmed pneumonia and venous thromboembolism	2
Silva-Pinto *et al*[31]	1	1
Total deaths	53	60

*Not all clinical diagnosis of ACS were subsequently confirmed on autopsy report.
ACS, acute chest syndrome

in this group of women but there is no evidence confirming it increases risk of thrombosis.[2 47]

Pulmonary complications contributed to the majority of maternal deaths, yet uncertainty remains regarding cause of death, particularly the pathogenesis of morbid complications in a disease where no diagnostic tissue pathology can be obtained in life. Complications including venous thromboembolism, amniotic fluid embolism, coagulopathy, PH, pneumonia, ACS and generalised sepsis can have overlapping clinical and imaging features (online supplementary table S3). Only a comprehensive autopsy can provide a true diagnosis[8]; this does not take place in many countries where SCD is most prevalent.

Pregnant women with SCD are at high risk of pulmonary complications and associated mortality. This review and meta-analysis provides contemporary prevalence estimates of ACS/pneumonia and PTE in this population. This information can be used to aid preconceptual counselling and to inform optimal management of SCD in pregnancy by highlighting the need for timely identification of pulmonary complications in this population. Delay in initiation of treatments and escalation of care have previously been identified by the confidential enquiry into maternal deaths as contributing to maternal deaths.[48] Further adequately powered research is needed to understand why HbSC genotype may be at similar risks of developing ACS/pneumonia during pregnancy to HBSS genotype. In addition, there is a paucity of data on the incidence of PH in pregnancies with SCD and in particular the management of PH. More work is needed to reduce the prepregnancy morbidities and occurrence of PH in women with SCD and there is an urgent need for studies to address how best to improve management of care of women with PH should they wish to continue with pregnancy. The prevalence of SCD is increasing globally. This review and meta-analysis should encourage renewed efforts to improve the clinical management, and thereby reduce the severe morbidity and mortality, of pregnant women with SCD.

Contributors This study was designed, directed and coordinated by EON and as the principal investigator, provided conceptual and technical guidance for all aspects of the project. SI and MB collected, analysed the data. PTS performed the statistical analysis. The manuscript was written by SI and MB and commented on by all authors (LO, SL and EO-N).

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