World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

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PREGNANCY CARE AND OUTCOMES IN SICKLE CELL DISEASE: A SYSTEMATIC REVIEW MAPPED AGAINST THE WHO 2025 GLOBAL GUIDELINE

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World Journal of Advanced Research and Reviews, 2026, 32(02), 353–366

Publication history: Received on 22 September 2026; revised on 01 November 2026; accepted on 03 November 2026

Article DOI: https://doi.org/10.30574/wjarr.2026.32.2.2780

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ABSTRACT

Background: Sickle cell disease (SCD) disproportionately impacts pregnancies in sub-Saharan Africa, but the World Health Organization (WHO) released its first global guidance for SCD in pregnancy in 2025. There is limited systematic evidence to support the outcomes of pregnancy in high-burden settings that meet these new recommendations.

Objective: To review and summarise existing evidence of maternal and perinatal outcomes in pregnancies complicated by SCD and to match reported care processes with the WHO 2025 recommendations.

Methods: This systematic review was conducted with a structure–process–outcome framework, according to PRISMA 2020. Observational studies and systematic reviews were identified from January 2015 to December 2025, using PubMed, Embase, Web of Science and Global Health. Studies reporting maternal or perinatal outcomes in women with HbSS/HbSC were eligible. Findings were synthesized narratively and plotted on the WHO recommendations 1a–1g.

Results: Fifteen sources were included: nine observational studies (7,579 SCD pregnancies or deliveries) and six evidence syntheses. SCD was consistently associated with elevated risks of preeclampsia (risk ratio [RR] 2.01, 95% CI 1.93–2.09), eclampsia (RR 2.62, 95% CI 2.35–2.92), venous thromboembolism (RR 10.79, 95% CI 9.52–12.22), and low birth weight (RR 1.85, 95% CI 1.75–1.96). The data from Nigeria revealed maternal mortality rates ranging from 0.3% to 20% and caesarean rates ranging from 21.6% to 80%. The mapping of guidelines identified a consistent lack of documentation for folic acid dosing, conditional iron supplementation, continuation of hydroxycarbamide, and assessment of thromboprophylaxis.

Conclusion: SCD in pregnancy is associated with substantially elevated risks of hypertensive disorders, thromboembolism, and adverse perinatal outcomes. There are important gaps in the evidence base on guideline-concordant care processes. Standardised outcome and process measures are much needed in prospective studies.

Keywords: Sickle Cell Disease; Pregnancy Outcome; WHO Guideline; Systematic Review; Nigeria

1 INTRODUCTION

Sickle cell disease (SCD) is one of the most prevalent inherited haemoglobin disorders in the world, with an estimated prevalence of 7.74 million people [1]. Malaria is endemic in areas of the world, especially in sub-Saharan Africa, where about 80% of the world's cases occur [2]. The world population of individuals with SCD more than doubled from 2000 to 2021, due to better survival to reproductive age [1, 3]. Nigeria has one of the highest national prevalence rates of SCD in the world, and significant mortality [4].

Women with SCD are at high risk during pregnancy. Women with SCD are 4-11 times more likely to die during pregnancy or childbirth than women without SCD, and this difference is even larger in low-income countries [2, 3]. A recent meta-analysis of 45 studies encompassing 38,386 SCD pregnancies and over 19 million control pregnancies confirmed markedly elevated risks of venous thromboembolism (risk ratio [RR] 10.79, 95% CI 9.52–12.22), preeclampsia (RR 2.01, 95% CI 1.93–2.09), eclampsia (RR 2.62, 95% CI 2.35–2.92), and low birth weight (RR 1.85, 95% CI 1.75–1.96) [5].

In June 2025, the World Health Organization released its first global guideline on the management of SCD during pregnancy, childbirth and the interpregnancy period [3]. The guideline provides 21 recommendations across the following areas: medication management, pain and fluid management, thromboprophylaxis, fetal monitoring, timing and mode of birth, and interpregnancy care [3]. This is especially important because the Guideline Development Group noted a lack of direct empirical evidence and recommendations were based on benefit–harm balance, equity, feasibility, and women's preferences, not on high-quality trial evidence [3]. The recommendations are: folic acid supplementation up to 5 mg daily outside malaria-endemic areas (or intermittent preventive treatment with sulfadoxine–pyrimethamine (IPT-SP) in the first trimester) [3]; iron supplementation only when deficiency is documented [3]; consider prophylactic transfusion in women with severe intractable crises [3]; continue or restart hydroxycarbamide after the first trimester, in shared decision-making [3]; and assess other thromboembolism risk factors [3]. Previous national guidance, including the British Society for Haematology guideline, was written mainly for high-income health systems [6].

Despite the well-known burden of SCD in pregnancy, there is a lack of systematic examination of how reported care processes align with the new WHO recommendations. Previous systematic reviews have concentrated on quantifying outcome risks [5, 7] and not examined guideline concordance. This is a consequential gap because it can help uncover actionable targets for quality improvement if it is identified where care is not aligned with evidence-informed recommendations.

1.1 Conceptual Framework

We used a conceptual framework based on Donabedian's structure–process–outcome model of health-care quality as applied to the evaluation of maternal care [8] to the clinical pathway of SCD in pregnancy (Figure 1). The framework links three components.

1.1.1 Structure (determinants and context)

The first is the biological and health system factors associated with pregnancy. Biologically, polymerisation of deoxygenated haemoglobin S results in the formation of rigid, fragile erythrocytes, which are responsible for vaso-occlusion, chronic haemolysis, endothelial dysfunction and hypercoagulable state [9]. Increased metabolic demand, physiological hypercoagulability and placental vasculopathy are all heightened during pregnancy, leading to an increased risk of vaso-occlusive crisis, hypertensive disorders, thromboembolism and impaired fetal growth [9, 10]. This risk is modified by the genotype (HbSS or HbSC). In the context, the endemicity of malaria, the timing of the booking of the antenatal period and the provision of multidisciplinary care, transfusion and laboratory services influence the type of care that can be provided, especially in low-income settings [3, 11].

1.1.2 Process (guideline-concordant care)

The second component consists of the care processes recommended by the WHO (1a-1g): folic acid supplementation in a context-appropriate manner, depending on the malaria endemicity (1a/1b); iron supplementation only when documented deficiency (1c/1d); prophylactic transfusion for severe intractable crises (1e); hydroxycarbamide continuation or commencement after the first trimester, with shared decision-making (1f); and assessment of other factors associated with thromboembolism, and initiation of thromboprophylaxis if indicated (1g). In the framework, these processes are the modifiable mechanisms by which the structural component can create a risk that can be reduced by health systems.

1.1.3 Outcome (maternal and perinatal)

The third component includes the maternal outcomes (hypertensive disorders, venous thromboembolism, maternal mortality, caesarean delivery, severe anaemia, infection, and vaso-occlusive crisis), and the perinatal outcomes (low

birth weight, preterm birth, stillbirth, perinatal mortality, and intrauterine growth restriction) reported in the literature.

The framework has a fourth, cross-cutting element: documentation. Guideline concordance can only be measured if a study reports on care processes. The framework thus implements the two strands of analysis of the review. The outcome synthesis is for the structure to outcome pathway (Objectives 1 and 2), while the guideline mapping is for the process component and documentation (Objective 3). The review was conducted and reported according to the PRISMA 2020 statement [12].

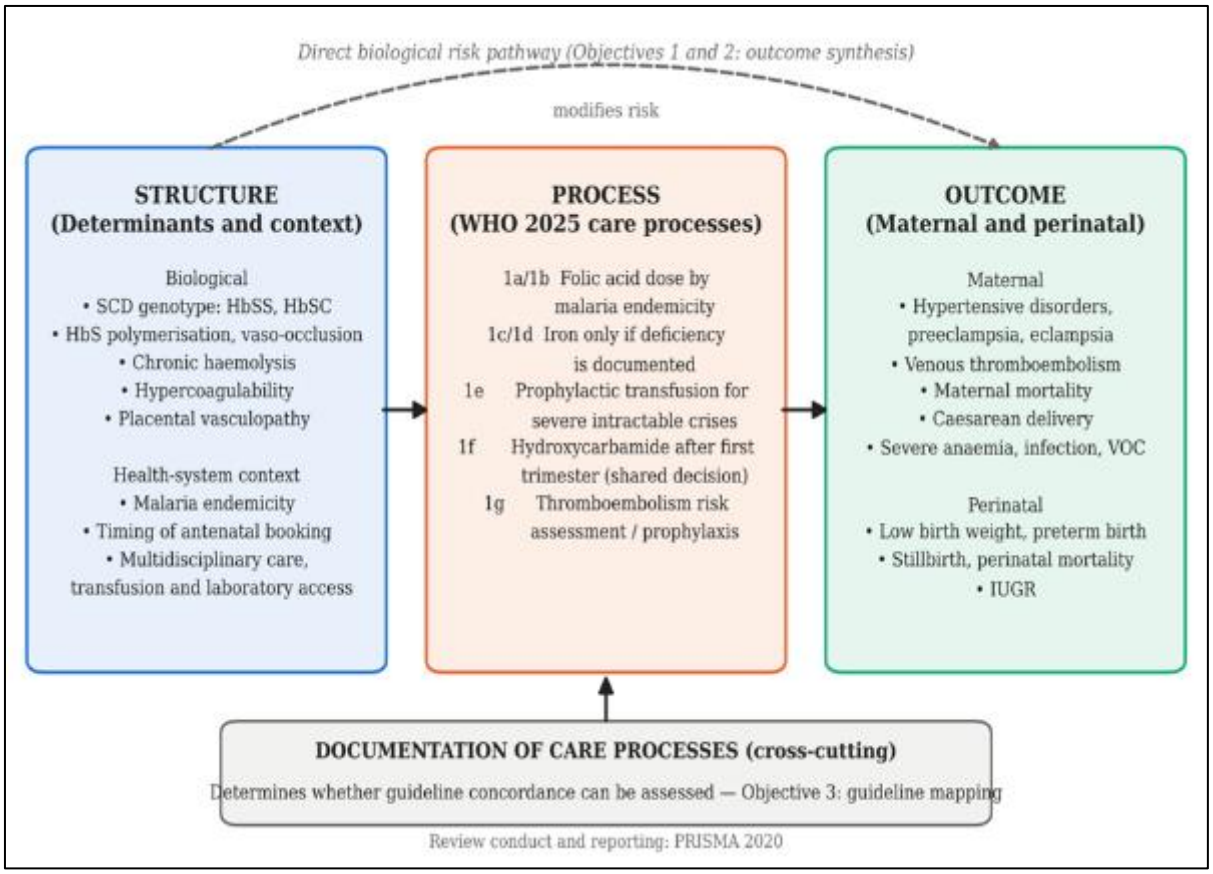


Figure 1: Conceptual framework of the review: structure–process–outcome pathway linking SCD pathophysiology and health-system context, WHO 2025 care processes (recommendations 1a–1g), and maternal and perinatal outcomes

1.2 Aim and Objectives

The aim of this systematic review was to synthesise the evidence on maternal and perinatal outcomes in pregnancies complicated by SCD and to evaluate the extent to which reported care aligns with the WHO 2025 recommendations. The specific objectives were to:

- Synthesise published evidence on maternal and perinatal outcomes in pregnancies complicated by SCD;
- Identify factors associated with adverse outcomes where reported; and
- Map documented care processes against the WHO 2025 recommendations to identify concordance and gaps.

2 MATERIALS AND METHODS

2.1 Study Design and Reporting

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [12] was followed to conduct and report this systematic review. Due to the expected variability in study designs, populations, and outcome definitions, a narrative synthesis approach was used.

2.2 Search Strategy

The databases PubMed, Embase, Web of Science and Global Health were searched between 1 January 2015 and 31 December 2025. Search strategy: Terms used were "sickle cell disease," "sickle cell anaemia," "HbSS," "HbSC," "haemoglobinopathy," AND "pregnancy," "pregnant," "obstetric," "maternal," "perinatal," AND "outcome," "mortality," "morbidity," "complication," "preeclampsia," "preterm," "low birth weight." Hand searching of reference lists of included sources was conducted for additional eligible reports

2.3 Eligibility Criteria

Sources were included if they: (1) were primary observational studies (cohort, case–control, cross-sectional, or before–after studies) or systematic reviews/meta-analyses of such studies that included pregnant women with confirmed SCD (HbSS or HbSC); (2) reported at least one maternal or perinatal outcome or a care process relevant to WHO recommendations 1a–1g; and (3) were published between January 2015 and December 2025. Case reports, narrative reviews, clinical guidelines and conference abstracts without extractable outcome data were not included. Guidelines and narrative reviews were used only as contextual sources and the WHO 2025 guideline was the reference standard for the guideline mapping [3].

2.4 Data Extraction and Quality Assessment

Data were screened and extracted by two reviewers independently. The methodological quality of primary observational studies was evaluated using the Newcastle-Ottawa Scale [13]. Study characteristics, outcomes, and documented care processes relevant to WHO recommendations were extracted.

2.5 Data Synthesis

A narrative synthesis was carried out. The number of participants was not aggregated across primary studies and syntheses, and the published pooled estimates from evidence syntheses were not re-pooled, because of the risk of double counting primary studies that were also included in the evidence syntheses. A care process was reported if the source reported it for its SCD pregnancy population. The process component of the conceptual framework (Figure 1) was followed when comparing the documented care processes descriptively with the WHO recommendations 1a–1g [3] for the guideline mapping.

3 RESULTS AND DISCUSSION

3.1 Study Selection

The search yielded 1,247 records. After removal of duplicates (n = 312), 935 titles and abstracts were screened. Of these, 87 full-text articles were assessed for eligibility; 72 were excluded for the following reasons: not SCD-specific (n = 28), no maternal or perinatal outcome reported (n = 19), ineligible study design (n = 15), and outside the date range (n = 10). Fifteen sources met the inclusion criteria: nine primary observational studies and six evidence syntheses (Figure 2).

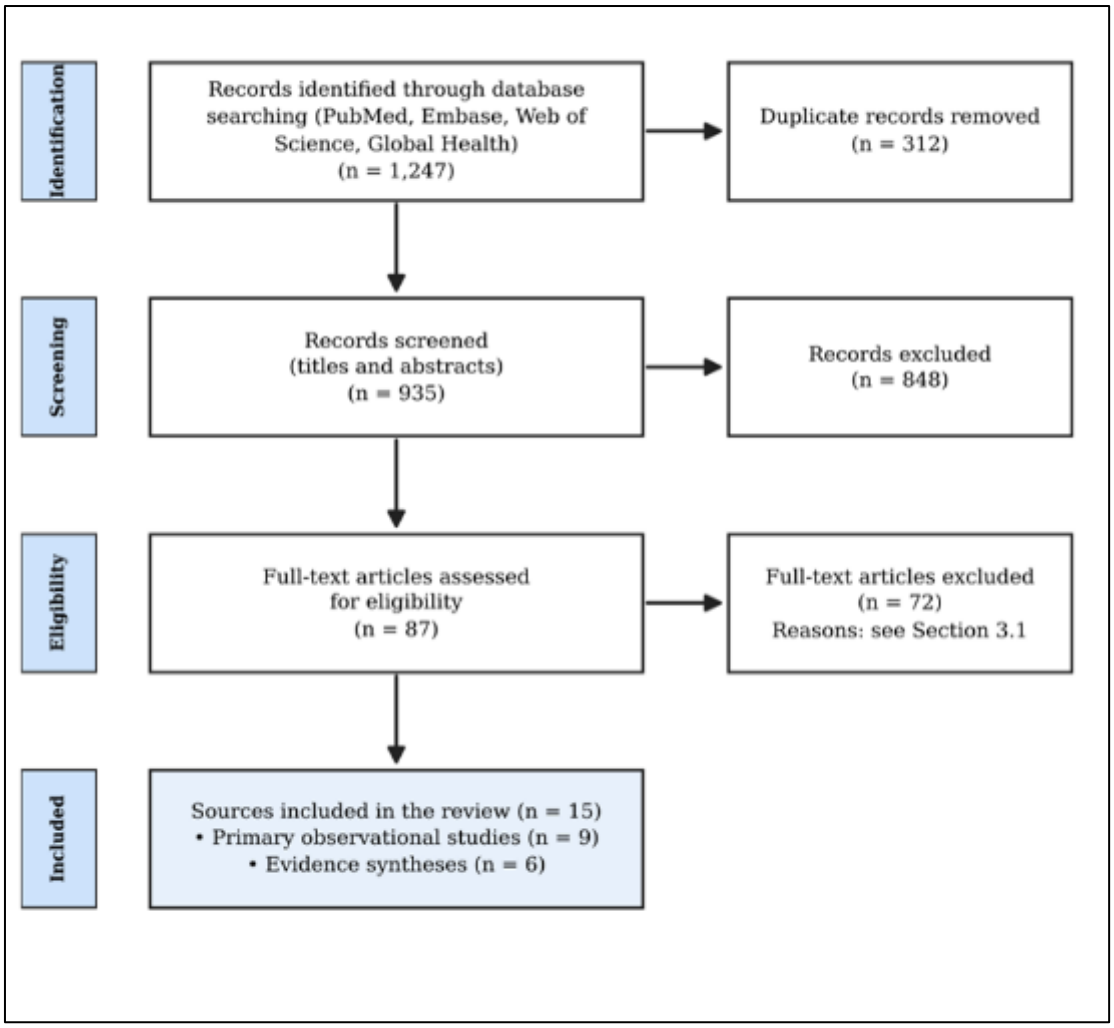


Figure 2: PRISMA 2020 flow diagram

3.2 Characteristics of Included Sources

There were 15 sources included, nine of which were primary observational studies and six evidence syntheses (Table 1). The primary studies included 7,579 pregnancies or deliveries with SCD in Ghana (n = 1), Nigeria (n = 2), the United States (n = 3), the United Kingdom (n = 1), and France (n = 1) with sample sizes ranging from 63 to 3,901. The evidence syntheses included a meta-analysis of 45 studies with 38,386 SCD pregnancies [5], a meta-analysis of 21 studies with 26,349 SCD pregnancies [7] and a meta-analysis of 16 studies from low and high income countries [14] as well as a systematic review of Nigerian data [16] and a systematic review of iron stores in pregnancy [17]. Participant numbers were not combined across the two groups since they can also be used for the syntheses.

Table 1: Characteristics of included sources (n = 15)

Author (Year) [Ref.]	Country	Design	SCD pregnancies (n)	Genotype distribution	Key outcomes reported
A. Primary observational studies (n = 9)					
Asare et al. (2017) [18]	Ghana	Before-and-after study (retrospective pre-, prospective post-intervention)	248 (158 pre, 90 post)	Not specified	Maternal mortality 10,791 to 1,176 per 100,000 live births after multidisciplinary care; perinatal mortality 60.8 to 23.0 per 1,000 births
Olukunle et al. (2024) [19]	Nigeria	Retrospective cohort	63	HbSS 63.5%, HbSC 36.5%	Maternal mortality 6.3%, anaemia 79.4%, VOC 55.6%, caesarean 46.1%, antepartum transfusion 39.7%
Oluwasola (2024) [20]	Nigeria	Retrospective cohort	106	HbSS 60.4%, HbSC 36.8%, HbCC 2.8%	Preeclampsia 27.3%, IUFD 27.3%, live births 84.9%
Early et al. (2023) [21]	USA	Retrospective (National Inpatient Sample)	3,901 deliveries	Not specified	Severe maternal morbidity aOR 7.22, VTE aOR 17.34, maternal mortality 13.3 per 10,000 deliveries
Della-Moretta et al. (2025) [22]	USA	Retrospective cohort	75	Not specified	VTE 7–13%, anticoagulation outcomes
Kroner et al. (2022) [23]	USA	Multicentre registry (cross-sectional)	1,788 pregnancies (241 HU-exposed)	Not specified	HU at conception and during pregnancy: miscarriage or stillbirth OR 2.21; term LBW OR 2.98
Oakley et al. (2022) [24]	United Kingdom	Matched cohort	131	Not specified	Preeclampsia/eclampsia aRR 3.53, preterm birth aRR 2.62, caesarean aRR 1.44
Corsia et al. (2025) [25]	France	Nationwide retrospective cohort	1,022 births	Not specified	Preeclampsia 9.6% vs 1.7%, caesarean 52.8% vs 18.2%, preterm birth 28.5% vs 5.6%; 308 women on long-term HU and/or transfusion
Habibi et al. — ESCORT-HU (2025) [26]	European multicentre	Prospective cohort	245 pregnancies	HbSS majority	About three-quarters of 178 pregnancies with known outcome ended in live birth; no HU-related malformations
B. Evidence syntheses (n = 6)					
Ifie et al. (2025) [5]	Multi-country	Meta-analysis (45 studies)	38,386	Variable	VTE RR 10.79, preeclampsia RR 2.01, LBW RR 1.85
Oteng-Ntim et al. (2015) [7]	Multi-country	Meta-analysis (21 studies)	26,349	HbSS, HbSC	HbSS: maternal mortality RR 5.98, stillbirth RR 3.94, preterm delivery RR 2.21
Boafor et al. (2016) [14]	Low- and high-income countries	Meta-analysis (16 studies)	Pooled	Variable	Maternal mortality OR 10.91, preeclampsia OR 2.05, IUGR OR 2.79

Malinowski et al. (2015) [15]	Multi-country	Meta-analysis (12 studies)	1,291 participants	Variable	Prophylactic transfusion: maternal mortality OR 0.23
Gbadebo et al. (2025) [16]	Nigeria	Systematic review and meta-analysis	Pooled Nigerian data	Variable	Maternal mortality 0.3–20%, caesarean 21.6–80%
Aroke et al. (2020) [17]	Multi-country	Systematic review	Pooled	HbSS, HbSC	Iron deficiency 6.67–83.33%; evidence inconclusive

VOC = vaso-occlusive crisis; IUFD = intrauterine fetal death; VTE = venous thromboembolism; LBW = low birth weight; IUGR = intrauterine growth restriction; HU = hydroxyurea; OR = odds ratio; RR = risk ratio; aOR = adjusted odds ratio; aRR = adjusted risk ratio.

3.3 Maternal Outcomes

Hypertensive disorders. The largest meta-analysis reported significantly increased risks of aggregated hypertensive disorders (RR 1.75, 95% CI 1.69–1.80), progressively higher risk ratios for pregnancy-induced hypertension (RR 1.10, 95% CI 1.03–1.17), preeclampsia (RR 2.01, 95% CI 1.93–2.09), and eclampsia (RR 2.62, 95% CI 2.35–2.92) [5]. A separate meta-analysis reported odds ratios of 2.05 (95% CI 1.47–2.85) for preeclampsia and 3.02 (95% CI 1.20–7.58) for eclampsia [14]. A London matched cohort found an adjusted risk ratio of 3.53 (95% CI 2.00–6.24) for preeclampsia or eclampsia [24] while a Nigerian cohort found that 27.3% of SCD pregnancies developed preeclampsia [20]. In a French national cohort, 9.6% of SCD pregnancies were reported as preeclampsia, versus 1.7% of control pregnancies [25].

3.3.1 Venous thromboembolism

The risk of VTE was markedly elevated (RR 10.79, 95% CI 9.52–12.22), with similarly high-risk ratios for deep vein thrombosis (RR 9.44, 95% CI 7.96–11.19) and pulmonary embolism (RR 10.00, 95% CI 8.16–12.25) [5]. One US retrospective study reported VTE rates of 7-13% in pregnant patients with SCD [22] and another US national inpatient analysis reported an adjusted odds ratio for VTE of 17.34 at delivery [21].

3.3.2 Maternal mortality

Maternal mortality rates were reported in Nigeria as varying between 0.3% and 20% [16]. The WHO guideline mentions that SCD can increase maternal mortality by 4-11 times [3]. A previous meta-analysis found a maternal mortality odds ratio of 10.91 (95% CI 1.83–65.11) compared with women without SCD [14] and an earlier meta-analysis found a relative risk of 5.98 (95% CI 1.94–18.44) for women with HbSS [7]. A combined SCD–obstetric multidisciplinary clinic in Ghana was correlated with a decrease in maternal mortality from 10,791 to 1,176 per 100,000 live births [18].

3.3.3 Caesarean delivery

In Nigeria, the rates of caesarean sections varied from 21.6% to 80% [16]. A London matched cohort found an adjusted risk ratio of 1.44 (95% CI: 1.18–1.76) for caesarean birth [24] and a French nationwide cohort reported caesarean delivery rates of 52.8% in pregnancies with SCD versus 18.2% in pregnancies without SCD [25]

3.3.4 Severe anaemia and infection

Nigerian data reported severe anaemia in 8.4% to 43.9% and infection in 1.5% to 41.6% [16]. Among 63 women in Nigeria, 79.4% were anaemic and 55.6% had a vaso-occlusive crisis [19].

Table 2: Maternal outcomes in SCD pregnancies: Comparative estimates and supporting or Nigerian data

Outcome	Comparative estimate (95% CI)	Source	Supporting estimate or Nigerian range	Source
Preeclampsia	RR 2.01 (1.93–2.09)	Ifie et al. [5]	OR 2.05 (1.47–2.85)	Boafor et al. [14]
Eclampsia	RR 2.62 (2.35–2.92)	Ifie et al. [5]	OR 3.02 (1.20–7.58)	Boafor et al. [14]
Venous thromboembolism	RR 10.79 (9.52–12.22)	Ifie et al. [5]	7–13% incidence	Della-Moretta et al. [22]
Maternal mortality	OR 10.91 (1.83–65.11)	Boafor et al. [14]	0.3–20%	Gbadebo et al. [16]
Caesarean delivery	aRR 1.44 (1.18–1.76)	Oakley et al. [24]	21.6–80%	Gbadebo et al. [16]
Severe anaemia	—	—	8.4–43.9%	Gbadebo et al. [16]
Vaso-occlusive crisis	—	—	55.6%	Olukunle et al. [19]

3.4 Perinatal Outcomes

- **Low birth weight.** Infants born to women with SCD had a significantly higher risk of being low birth weight (RR 1.85, 95% CI 1.75–1.96) [5]. A separate meta-analysis reported a low-birth-weight odds ratio of 2.00 (95% CI 1.42–2.83) [14].
- **Preterm birth.** The rate of premature birth reported in Nigeria ranged from 16.3% to 75.4% [16]. A relative risk of 2.21 (95% CI 1.47 to 3.31) was reported for women with HbSS in the meta analysis [7] and an adjusted risk ratio of 2.62 (95% CI 1.82 to 3.78) was reported in a matched cohort in London [24].
- **Stillbirth and perinatal mortality.** The rate of stillbirths in Nigerian studies varied from 2.5% to 25.5% while the rate of perinatal mortality ranged from 2.1% to 20.9% [16]. Meta-analysis reported a relative risk of stillbirth of 3.94 (95% CI 2.60–5.96) for women with HbSS [7] and a perinatal mortality odds ratio of 3.76 (95% CI 2.34–6.06) [14]. Intrauterine fetal death was found to be 27.3% in Nigerian cohort [20].
- **Fetal growth restriction.** In Nigeria, the prevalence of IUGR ranged from 5.1% to 50% in various studies [16] and the odds ratio was 2.79 (95% CI 1.85–4.21) in the meta-analysis [14].

Table 3: Perinatal outcomes in SCD pregnancies

Outcome	Comparative estimate (95% CI)	Source	Supporting estimate or Nigerian range	Source
Low birth weight	RR 1.85 (1.75–1.96)	Ifie et al. [5]	OR 2.00 (1.42–2.83)	Boafor et al. [14]
Preterm birth	RR 2.21 (1.47–3.31)†	Oteng-Ntim et al. [7]	16.3–75.4%	Gbadebo et al. [16]
Stillbirth	RR 3.94 (2.60–5.96)†	Oteng-Ntim et al. [7]	2.5–25.5%	Gbadebo et al. [16]
Perinatal mortality	OR 3.76 (2.34–6.06)	Boafor et al. [14]	2.1–20.9%	Gbadebo et al. [16]
IUGR	OR 2.79 (1.85–4.21)	Boafor et al. [14]	5.1–50%	Gbadebo et al. [16]

IUGR = intrauterine growth restriction. †Estimate for women with HbSS genotype.

Figure 3 summarises the comparative relative risk estimates for maternal and perinatal outcomes reported in Tables 2 and 3. All estimates lie above the line of no effect, and the largest relative risks were observed for venous thromboembolism and maternal mortality.

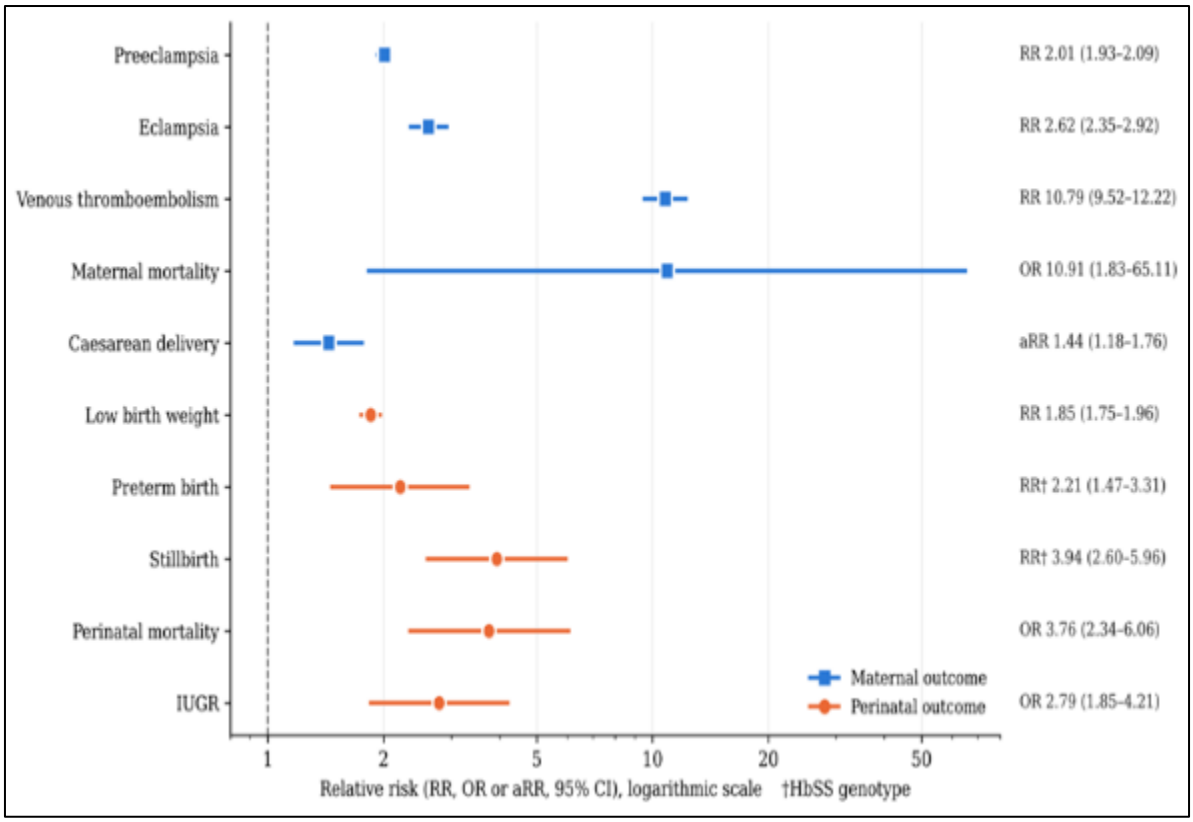


Figure 3: Relative risk estimates (RR, OR or aRR with 95% CI, logarithmic scale) for maternal and perinatal outcomes in pregnancies with SCD vs. pregnancies without SCD. Data from Ifie et al. [5], Boafor et al. [14], Oteng-Ntim et al. [7] and Oakley et al. [24], as reported in Tables 2 and 3

3.5 Mapping Against WHO Recommendations

Seven of the 15 sources reported at least one care process that could be aligned with WHO recommendations 1a–1g (Table 4; Figure 4). All domains of medication management covered in recommendations 1a-1g were not reported by any source.

3.5.1 Folic acid supplementation (1a/1b).

No source in the included literature reported a dose of folic acid in relation to malaria endemicity and intermittent preventive treatment with sulfadoxine–pyrimethamine [3].

3.5.2 Iron supplementation (1c/1d).

A systematic review was one source on iron status and supplementation. It concluded that the evidence of iron stores in pregnant women with SCD is still limited and inconclusive, with prevalence of iron deficiency ranging from 6.67% to 83.33% in small studies, and that one randomised trial found no difference in outcomes between supplemented and unsupplemented women [17]. No primary study compared supplementation when the deficiency is documented with universal prophylaxis. The WHO guideline clearly states that iron supplementation is not indicated unless iron deficiency is proven [3] and iron overload is a known problem, especially in transfusion recipients [27].

3.5.3 Prophylactic transfusion (1e).

Transfusion practices were reported from three sources. In Nigeria, 39.7% of women needed transfusion during the antepartum period, primarily women who were not registered for antenatal care, suggesting that transfusion was not used as a prophylactic measure [19]. A French nationwide cohort found 308 women receiving long-term treatment with hydroxyurea and/or a transfusion programme [25]. A meta-analysis of prophylactic transfusion demonstrated reduced odds of maternal mortality (OR 0.23, 95% CI 0.06–0.91), vaso-occlusive pain crises (OR 0.26, 95% CI 0.09–0.76), and perinatal mortality (OR 0.43, 95% CI 0.19–0.99) [3, 15]. The criteria for prophylactic versus reactive transfusion, however, varied in the sources.

3.5.4 Hydroxycarbamide continuation (1f).

Concordance with recommendation 1f was not assessed as there were no reports of continuation or recommencement after the first trimester of pregnancy for three sources of hydroxycarbamide (HU) exposure in pregnancy. In a US multicentre registry, 241 pregnancies were conceived on HU, with HU use at conception and during pregnancy associated with miscarriage or stillbirth (OR 2.21, 95% CI 1.40–3.47) and birth weight < 5.5 lb in term infants (OR 2.98, 95% CI 1.09–7.38) [23]. The ESCORT-HU cohort reported 245 pregnancies with HU exposure; approximately three-quarters of the 178 pregnancies with known outcome resulted in live birth and no malformations associated with HU were observed [26]. The French group reported long-term HU treatment (no indication of timing in pregnancy) [25]. A systematic review of the safety of HU in pregnancy found that risks are not as high as previously thought and that there may be a benefit to use, given the high risk of untreated SCD [28, 29].

3.5.5 Thromboprophylaxis assessment (1g).

Table 4: Guideline mapping: Reported care processes against WHO recommendations

WHO recommendation	Sources reporting (n = 15)	Documentation quality	Concordance assessment
1a/1b: Folic acid (appropriate dose)	0	Dose and malaria context not documented	Evidence gap
1c/1d: Iron only if deficient	1 (Aroke et al. [17])	Deficiency criteria variable; no primary study reported them	Gap
1e: Prophylactic transfusion	3 (Olukunle et al. [19]; Corsia et al. [25]; Malinowski et al. [15])	Prophylactic vs on-demand criteria inconsistently defined	Partial
1f: Hydroxycarbamide continuation	3 (Kroner et al. [23]; Habibi et al. — ESCORT-HU [26]; Corsia et al. [25])	Exposure reported; continuation after first trimester and shared decision-making not reported	Indeterminate
1g: Thromboprophylaxis assessment	1 (Della-Moretta et al. [22])	Anticoagulation reported; risk assessment not documented	Evidence gap

Seven of the 15 sources reported at least one care process; a source may contribute to more than one recommendation.

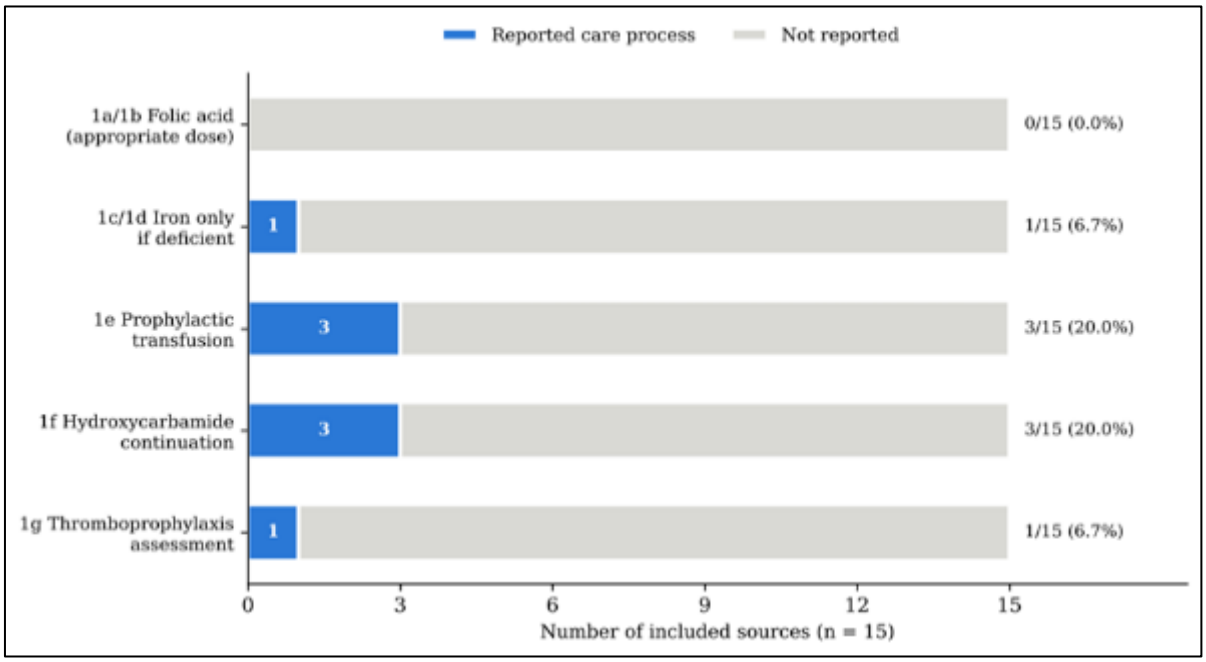


Figure 4: Number of included sources (n = 15) reporting care processes corresponding to each WHO 2025 medication-management recommendation (1a–1g). Data from Table 4

There was one source reporting anticoagulation practice and no source reporting systematic thromboprophylaxis risk assessment. In a retrospective US study, there was no statistically significant increase in PPH or bleeding complications

with the use of prophylactic anticoagulation, but there was an increase in VTE events in the anticoagulated group compared to the non-anticoagulated group (10% vs 0%) [22].

3.6 Principal Findings

This systematic review provides a synthesis of evidence from 15 sources, including nine primary observational studies with 7,579 SCD pregnancies or deliveries, and six evidence syntheses, and confirms that SCD is associated with significantly higher risks of hypertensive disorders, venous thromboembolism, adverse perinatal outcomes and maternal mortality. The most salient result is the lack of reported care process data to enable meaningful assessment of guideline adherence. Only seven of the 15 sources reported any information about the care process and none of the sources systematically documented all domains addressed by the WHO recommendations.

The results obtained are consistent with previous syntheses. Meta-analysis by Ifie et al. gives the latest and most complete estimates, showing a risk of VTE nearly eleven times higher and of preeclampsia two times higher [5]. The results are consistent with the London matched cohort which found adjusted risk ratios of 3.53 for preeclampsia or eclampsia and 2.62 for preterm birth [24]. They highlight the clinical need for thromboprophylaxis assessment (recommendation 1g) and hypertension surveillance. The Nigerian data show that maternal mortality rates vary from 0.3% to 20% and the caesarean rate 21.6% to 80%, suggesting that the quality of care and the case mix are different in the various settings.

3.7 Guideline Concordance and Evidence Gaps

The most significant result of this review is not an outcome measure, but a lack of one: there is little evidence of any reported care processes that could be used to determine if the WHO recommendations are being followed. The process component (the modifiable link between structural risk and outcomes) is the least visible component in the published literature, in terms of the conceptual framework (Figure 1).

First, as far as folic acid supplementation is concerned, the WHO guideline draws a distinction that is context specific, depending on the malaria endemicity [3]. The 400 μg dose is recommended for women who are taking intermittent preventive treatment with sulfadoxine-pyrimethamine in malaria-endemic areas like Nigeria [3]. Folic acid studies without dose and context information cannot guide to implementation of guidelines.

Secondly, the practices of iron supplementation seem inconsistent with the WHO recommendations. The recommendation to only prescribe iron when deficiency is documented [3] is based on evidence that iron overload is a problem in SCD, especially in transfused patients [27]. Since there are no primary study reports included that provide deficiency-based criteria, it is not possible to determine if practice meets this recommendation.

Third, it is significant that very little hydroxycarbamide continuation data has been reported. In the shared decision making, the WHO recommendation (1f) clearly states that continuation or recommencement after the first trimester is supported. The ESCORT-HU cohort reported reassuring safety data, with approximately three-quarters of pregnancies with known outcome being live births and no malformations reported as related to HU, but did not report guideline-concordant continuation [26]. In contrast, a US multicentre registry found increased risk of miscarriage or stillbirth in women who were treated with hydroxyurea at conception and during pregnancy, highlighting the importance of shared decision making and routine monitoring of outcomes [23].

Fourth, the lack of data on thromboprophylaxis assessment is of great concern because of the size of the VTE risk shown by Ifie et al. [5]. The 10-fold higher risk of thromboembolism should be a call for systematic risk assessment and consideration of venous thromboembolism prophylaxis, as suggested by previous meta-analytical data that showed an association between SCD and venous thromboembolism [30]. A recent U.S. study did not show significant bleeding risks with prophylactic anticoagulation, which means that thromboprophylaxis should be considered in this population [22].

3.8 Implications for Research and Practice

There is a need for research that reports both outcome and care processes, with standardised definitions in line with WHO recommendations. Evidence to assess implementation of guidelines would be provided by prospective cohort studies and registry-based analyses that would include information on medication management, transfusion practices and thromboprophylaxis assessment.

The current outcome data provide support for some immediate actions for practice. Systematic monitoring for the development of hypertensive disorders and documented risk assessment of thromboprophylaxis should be standardised in the antenatal care of women with SCD, given the consistent evidence of increased risk of preeclampsia and VTE [10].

Limitations

There are some limitations of this review. First, the study designs and outcome definitions were not uniform, making the pooling of results using a meta-analysis not feasible for most of the outcomes; structured reporting of synthesis without meta-analysis would benefit future syntheses [31]. Second, the lack of reporting of the care process makes the mapping of the guideline based on a limited number of studies. Third, publication bias may have favoured studies reporting significant associations. Fourth, one included study [20] also reported a small proportion of HbCC pregnancies (2.8%), which was retained because the majority of the cohort was HbSS/HbSC.

4 CONCLUSION

This systematic review confirms that SCD in pregnancy is linked to significantly higher rates of hypertensive disorders, venous thromboembolism, adverse perinatal outcomes and maternal death. The most important result, however, is the almost complete lack of reported care process data in line with the WHO 2025 recommendations. There are critical gaps in evidence for folic acid dosing in malaria-endemic settings, conditional iron supplementation, hydroxycarbamide continuation and assessment of thromboprophylaxis. These gaps have to be filled with research (systematically reporting guideline-concordant care processes) and practice (implementation of protocolised assessment and documentation).

Recommendations

- **Standardise reporting of care processes** in future studies of SCD in pregnancy, such as folic acid dose, malaria context, iron supplementation criteria, hydroxycarbamide use and assessment of thromboprophylaxis.
- **Implement routine thromboprophylaxis risk assessment** for all pregnant women with SCD, as there is an approximately ten-fold increase in the risk of VTE
- **Conduct an audit of iron supplementation practices** in line with the WHO guidelines that iron supplementation is recommended only when iron deficiency is documented
- **Establish prospective registries** capturing both outcomes and care processes.
- **Prioritise early antenatal booking** through community engagement.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Acknowledgments

The authors thank the World Health Organization for open access to its 2025 guideline, and the contributors of the primary studies and evidence syntheses included in this review.

Disclosure of conflict of interest

The authors declare no conflicts of interest.

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