# A systematic critical appraisal of evidence-based clinical practice guidelines for the management of pregnant women with sickle cell disease using the Appraisal of Guidelines for REsearch and Evaluation II (AGREE II) instrument.

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**Abstract**

Rationale, aims, and objectives: Management of pregnant women with sickle cell disease (SCD) represents a challenge to maternal healthcare services due to its potential complications with associated morbidity and mortality. Trustworthy evidence-based clinical practice guidelines (CPGs) have a major impact on supporting appropriate healthcare positive outcomes. The objective of this study was to critically appraise the quality of recent CPGs for SCD in pregnancy. Methods: We identified clinical questions and eligibility criteria, searched, and screened for CPGs using CPG databases, DynaMed, PubMed, and Google Scholar. Each included CPG was appraised by four independent appraisers using the Appraisal of Guidelines for REsearch & Evaluation II (AGREE-II) instrument. An additional inter-rater analysis was conducted. Results: Four eligible CPGs were appraised: American College of Obstetricians and Gynecologists (ACOG); National Heart, Lung, and Blood Institute (NHLBI); National Institute of Health and Care Excellence (NICE); and Royal College of Obstetricians and Gynaecologists (RCOG). The AGREE-II standardized domain scores revealed variation between the quality of these CPGs. Overall, the recommendations were not significantly different between these four CPGs. Conclusions: In recent years, there has been an improvement in the reporting of CPG development methodology. CPG development working groups should aim to adhere to the AGREE II criteria to improve the standards and quality of CPGs. RCOG followed by NHLBI CPGs showed the highest quality and were strongly recommended. We recommend incorporating AGREE-II appraisal of CPGs in the education of obstetricians, gynecologists and hematologists to guide their selection of CPGs for their daily practice.

**Keywords to aid indexing:**

Sickle cell disease, pregnancy, practice guidelines, AGREE II instrument, quality assessment.

## Introduction

Sickle cell disease (SCD) is a genetic disorder that leads to vaso-occlusive phenomena and hemolysis and a myriad of other major complications that could be life-threatening. It is one of the commonest inherited diseases globally and is inherited as an autosomal recessive disease caused from the substitution of valine for glutamic acid at the sixth amino acid of the beta-globin chain. [1] This amino acid substitution leads to the production of a hemoglobin that is poorly soluble when deoxygenated. The clinical features such as vaso-occlusive phenomena, results from the polymerization of deoxygenated hemoglobin S. In pregnancy, SCD is associated with significant maternal morbidity and mortality. The recognized complications include

maternal mortality, preeclampsia, eclampsia, venous thromboembolism, cesarean delivery, intrauterine fetal death and fetal growth restriction.[2]

The prevalence of SCD varies between countries. For example, data from the United States showed that the overall prevalence is roughly about 4.83 per 10,000 deliveries.[3] Among those women with SCD, 28.5% of them develop a crisis at the time of delivery. The maternal mortality rate was reported to be 1.6 per 1000 deliveries in women with SCD, compared to 0.1 per 1000 without SCD.[3]

Information about the prevalence in Saudi Arabia is probably underestimated and varies between the different provinces, with the highest prevalence being in the Eastern province, followed by the Southwest province.[4]

SCD in pregnancy tends to cause higher episodes of painful crises and a higher frequency of blood transfusion2. Although complications of SCD are more commonly associated with genotype HbSS, other genotypes such as: HbSB and HbSC, are considered part of SCD and should receive the same level of care as those with HbSS. The development of a multidisciplinary care approach and comprehensive sickle cell centers seem to be associated with a decrease in the incidence of perinatal complications.[5,6]

To date, in Saudi Arabia, there is no National Clinical Practice Guidelines to provide guidance for management of SCD in pregnant women.

Clinical Practice Guidelines (CPGs) were defined, by the Health and Medicine Division (HMD) of the American National Academies, formerly the Institute of Medicine (IOM), as 'statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.[7]

The Second edition of the Appraisal of Guidelines for Research and Evaluation Instrument (AGREE II) is the gold standard for quality assessment or critical appraisal of CPGs. It was first published in its original form in 2003 and lastly updated in 2017 by the AGREE enterprise. AGREE II is a validated quantitative tool that has been cited in well over 1013 articles and endorsed by several healthcare organizations.[8,9]

AGREE II identifies constituents that must be addressed by CPGs to improve their quality and henceforth ensure their expected trustworthiness and positive impact on healthcare outcomes.[9]

We decided as a university referral teaching hospital to take the initiative and conduct a systematic review of published evidence-based CPGs and critically appraising eligible CPGs using the AGREE II instrument in preparation for adapting a CPG for management of pregnant women with SCD as part of our CPG adaptation program that follows a formal methodology for adaptation of CPGs, the '*King Saud University Modified ADAPTE* ' method, where details of which were reported in a previously published article.[10]

## Methods

The protocol for this study was published to the PROSPERO (International prospective register of systematic reviews). Link: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=145443 .[11]

### Eligibility criteria

We included CPGs for SCD in pregnancy that: (1) were evidence-based CPGs with a clear and detailed documentation of the CPG development methods; (2) were in English language; (3) were original Source CPGs (de novo developed); (4) were national or international CPGs; (5) published between January 1, 2014 and December 30, 2018 and the search was repeated before the final manuscript submission to identify any new relevant CPGs; (6) were published by an organization or group authorship in a CPG database or peer-reviewed journal. Only the most current version of each Source CPG was included.

We excluded CPGs that were published earlier than 2014, written in a non-English language, adapted from other Source CPG(s), presented as consensus or expert-based statements, or that had a single author.[11]

### Search, screen, and selection of SCD in pregnancy CPGs

We used literature searches of bibliographic databases (Medline/PubMed and Google Scholar), EBSCO DynaMed Plus (USA), and relevant CPG databases: the ECRI Institute Guidelines Trust, National Institute of Health and Care Excellence (NICE; UK), Guidelines International Network (G-I-N) International guideline library, Scottish Intercollegiate Guidelines Network (SIGN; UK), and the Australian National Health and Medical Research Council (NHMRC; Australia). Moreover, we searched databases of national and international societies specializing in fields related to our health topic of SCD in pregnancy like the American College of Obstetricians and Gynecologists (ACOG), Royal College of Obstetricians and Gynaecologists (RCOG), Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), Society for Maternal Fetal Medicine (SMFM), Saudi Society for Obstetrics and Gynecology (SSOG), and Arab Association of Obstetrics and Gynaecology Societies (FAGOS). Keywords used included "sickle cell disease" AND "pregnancy" OR "pregnant women" AND "guideline," "practice guideline," "clinical practice guideline," "practice parameter," "guidance," OR "recommendations".[11]

The PubMed electronic search strategy included; ("anemia, sickle cell"[MeSH Terms] OR ("anemia"[All Fields] AND "sickle"[All Fields] AND "cell"[All Fields]) OR "sickle cell anemia"[All Fields] OR ("sickle"[All Fields] AND "cell"[All Fields] AND "disease"[All Fields]) OR "sickle cell disease"[All Fields]) AND "pregnan"[All Fields] AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields]) OR ("pregnant women"[MeSH Terms] OR ("pregnant"[All Fields] AND "women"[All Fields]) OR "pregnant women"[All Fields]) AND ("guideline"[Publication Type] OR "guidelines as topic"[MeSH Terms] OR "guidelines"[All Fields]) AND (Practice Guideline[ptyp] AND ("2014/01/01"[PDAT] : "2019/12/31"[PDAT]) AND "humans"[MeSH Terms]). Furthermore, we used the PIPOH (Patient Population, Interventions, Professionals, Outcomes, and Healthcare Setting) model to support the CPG eligibility process.[10] Three reviewers (YA, MA, YS) screened titles and abstracts of retrieved CPGs and articles meeting the inclusion criteria independently. The screening was re-checked by three different reviewers (GE, AA, OK). Disagreements were resolved by focus group discussions within the whole group after retrieval and review of the full-text articles or full CPG documents, including links to any accessible online supplementary documents or web resources. The search was repeated before the final manuscript submission to retrieve any new eligible CPG.

**Assessment of CPGs using the AGREE II Instrument**

The AGREE II Instrument (www.agreetrust.org) consists of 23 items organized in 6 domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence.[12] Each item is scored on a 1-7 Likert scale. The AGREE II evaluation was guided by utilizing its online version; "My AGREE PLUS" that supports having a CPG "appraisal group" for each CPG that compiles and calculates the items' ratings into domain ratings, and comments.[12] The four AGREE II appraisers hold the relevant clinical expertise in obstetrics and gynecology (YS, AA), internal medicine and hematology (GE, MA), in addition to an expert CPG methodologist (YA). At the outset, the CPG methodologist conducted capacity building sessions for the reviewers through hands-on sessions in the concepts, evidence-based CPGs' standards, and using the AGREE II instrument. Each reviewer scored his/her assigned CPGs. Each one of the included CPGs was critically appraised by all of the five reviewers. All appraisers reviewed the full CPG documents including any updates plus any relevant supplementary information or links to online webpages related to the CPG methods or CPG implementation tools. For each item, AGREE appraisers were asked to record the justifications for their scores in the 'Comment' section. Wide discrepancies between the assessors' scores were resolved by asking those who had provided outlying scores to re-assess after discussion with the entire group. The standardized AGREE domain scores or ratings (%) were automatically calculated by online My AGREE PLUS. We agreed upon a cut-off point of 70% for each AGREE standardized domain score or rating. After the appraisal, more weight was emphasized on the scores of domains 3 and 5 to facilitate the filtration and final evaluation of the reporting quality of eligible CPGs. Similar cut-off values were reported.[13,14] In addition to the classification of the six AGREE II domains, the evidence-base of the included CPGs, their references sections, were screened for systematic reviews or meta-analyses specifically Cochrane reviews. We utilized the PRISMA statement flow diagram and checklist' in the reporting our review.[15-17] There was no patient nor public involvement in this review.

### Inter-rater analysis

We conducted inter-rater reliability assessment tests (IRR), to determine the agreement level between raters. We used % agreement IRR for every question in each domain in the four eligible SCD in pregnancy CPGs to assess the level of agreement among the four raters as well as the percent agreement of the first overall assessment (OA1) of the AGREE II Instrument. Moreover, we used the Intra-class correlation and measured the consistency of ratings or capacities for datasets that have been gathered as clusters or arranged into clusters including the second overall assessment (OA2 or 'recommend this CPG for use'). Intra-class correlation (ICC) is one of the most prevalent IRR approaches that is used when we have more than two raters. We used it as we had more than a couple of pairs. A high Intra-class-Correlation-Coefficient (ICCC or Kappa) near one specified high resemblance between standards from the same set. A low Kappa value near zero indicated that standards from the same set are not alike. We used ANOVA "One-Way Random" on SPSS Statistics, version 21 because we had inconsistent raters/rates. The diversity of numerical data from groups or clusters, drove us to use ICCC. This helped us in detecting reproducibility as well as how closely peers resemble each other regarding to certain traits or characteristics. We evaluated the agreement between two ordinal scale classifications. Henceforth, we used Weighted Kappa (Quadratic Weights) because the data came from an ordered scale.

We used linear weights as the difference between the first and second category had the same importance as the difference between the second and third category, and so on. Agreement was quantified by the Kappa (K) statistic.[18,19] where K equals 1 when there is perfect agreement between the classification systems; K equals 0 when there is no agreement better than chance; and K is negative when agreement is worse than chance. The K value can be interpreted as shown in Table 1.[20]

### Identification of SCD in pregnancy CPGs

We summarized the results of the search in the PRISMA statement flow diagram shown in Figure 1.[16-18] The initial list of 96 found CPGs was reviewed and filtered by the assessors. Of these, 92 were excluded based on the eligibility criteria. Furthermore, four recent SCD in pregnancy CPGs complied with our PIPOH and inclusion criteria as shown in Figure 1. These CPGs were developed by ACOG in January 2007 (reaffirmed in 2018)[21], NICE in June 2012 (with a minor update in August 2016)[22], RCOG in August 2011 (updated in May 2018)[23], and the US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute in 2014.[24]

### Key characteristics of SCD in pregnancy CPGs

Table 2 highlights the characteristics of all eligible CPGs that included four national CPGs (ACOG, NHLBI, NICE, and RCOG). Three CPGs were developed by US-based (n=3, 75%), and one CPG (n=1, 25%) by UK-based organizations. The four included CPGs were developed by two reference specialized professional organizations (ACOG, RCOG), and two national evidence-based healthcare improvement organizations (NICE, NHLBI).[21-24]

### Reporting the quality of SCD in pregnancy CPGs

The AGREE II standardized domain ratings were summarized in Table 3 and the appraisers' comments were reported in Table 4.

### Domain 1: Scope and purpose

The AGREE II standardized score for domain 1 ranged from 76% to 93%. Scores of three CPGs were greater than 70% in domain 1 (NICE-2012=93%, RCOG-2018=89%, NHLBI-2017=88%).

### Domain 2: Stakeholder involvement

The AGREE II standardized domain scores for domain 2 ranged from 33% to 85%. Scores of two CPGs were greater than 70% in domain 2 (NICE-2016=85%, RCOG-2018=76%).

### Domain 3: Rigor of development

The AGREE II standardized scores for domain 3 ranged from 41% to 90%. Scores of three CPGs were greater than 70% in domain 3 (NICE-2016=90%, RCOG-2018=73%, NHLBI-2017=71%).

**Domain 4: Clarity of presentation**

The AGREE II standardized scores for domain 4 ranged from 63 % to 89%. Scores of three CPGs were greater than 70% in domain 3 (NICE-2016=89%, RCOG-2018=83%, NHLBI-2017=83%).

**Domain 5: Applicability**

The AGREE II standardized scores for domain 5 ranged from 24% to 90%. Only one CPG was scored greater than 70% in domain 5 (NICE-2016).

**Domain 6: Editorial independence**

The AGREE II standardized scores for domain 6 ranged from 19% to 77%. Scores of two CPGs were greater than 70% in domain 6 (RCOG-2018=76%, NICE-2016=85%).

**Overall assessment**

The AGREE II standardized domain scores for the first overall assessment ranged from 46% to 83%. Three CPGs scored greater than 70% (NHLBI, NICE, RCOG) that was consistent with their higher scores in the six AGREE II domains. Calculated AGREE II domain scores are shown in Figures 2 and 3. These radar maps illustrate the final scores for every eligible CPG in each of the six domains in Figure 2 and each of the 23 questions in Figure 3, expressed as a percentage. Higher standardized domain scores are mapped towards the periphery (closer to 100%), and lower domain scores are plotted towards the center. The graphs illustrate a visual display of the relative strengths or weaknesses of each CPG by domain, question, and the OA1 in comparison to the other plotted CPGs.

**Recommending the SCD in pregnancy CPGs for use in practice**

The second (overall) assessment, regarding the recommendation for using the CPG in practice, revealed a consensus agreement between the reviewers on recommending the use of two of the appraised CPGs without modification including the RCOG and NHLBI CPGs and the other two CPGs with modifications (NICE, RCOG).

Strengths and limitations of the included CPGs are summarized in Table 4 based on the consensus and comments of the CPG appraisers for each item of the AGREE II.

All of the included CPGs cited systematic reviews in their references list. The largest number of systematic review citation was observed in the RCOG CPG (N=6) among them five were Cochrane reviews (83%). Overall, the lines of management of pregnant women with SCD were similar in these CPGs as shown in Table 5.

**Inter-rater analysis (IRR)**

The results of the IRR tests, showed high strength of agreement, for every question in every domain in the four practice guidelines among the four raters. As well as the percent agreement of the first overall assessment (OA1) in Figure 2. Most of the Kappa values were between (0.50-1.00) denoting good to excellent agreement. Two evaluations only shown in Figure 3, revealed poor strength of agreement (K=0.0). ACOG, D2Q3 and D3Q2. ACOG evaluation showed one question out of 24 with excellent agreement (K=1), 16 questions with good agreement (K=0.5), 5 questions with very good agreement (K=0.6-0.8), two questions with poor agreement (K=0.00) and the overall assessment (1) showed good agreement (K=0.5). RCOG 2011 evaluation showed no questions out of 24 with excellent agreement, 15 questions with good agreement (K=0.5), nine questions with very good agreement (K=0.6-0.8) and the overall assessment (1) showed good agreement (K=0.5). NICE 2012 evaluation showed one question out of 24 with excellent agreement (K=1), no questions with fair agreement, 16 questions with good agreement (K=0.5), seven questions with very good agreement (K=0.6-0.8), and the overall assessment (1) showed good agreement (K=0.5). NHLBI evaluation

showed no questions out of 24 with excellent agreement, 15 questions with good agreement (K=0.5), nine questions with very good agreement (K=0.6-0.8) and the overall assessment (1) showed good agreement (K=0.5). Table 6. Intra class correlation coefficient (Kappa value) among raters for the four guidelines regarding the second Overall Assessment (OA2), showed the following; Number of observed agreements: 6 (37.50% of the observations). Number of agreements expected by chance: 4.0 (25.00% of the observations). Kappa= 0.167. SE of kappa = 0.138. 95% confidence interval: From -0.103 to 0.437, Weighted Kappa= 0.077.

**Discussion**

To the best of our knowledge, this is the primer review that systematically evaluates the quality of recently published CPGs of SCD in pregnancy using the AGREE II instrument.

Four CPGs addressing the management of pregnant women with SCD were assessed using the AGREE II instrument. This AGREE II assessment highlighted several areas of improvement in the methodological rigor of the included CPGs. One CPG (ACOG) had significant gaps in its rigor of development (Domain 3), which is the largest and core domain, and three CPGs demonstrated areas for improvement in their applicability (Domain 5). The weight of these two domains has been emphasized. The NICE CPG received the highest reviewer agreement ratings.[22] All of the four included CPGs had commonalities and differences in their clinical recommendations and are summarized in Table 5. Commonalities included genetic screening (ACOG, RCOG), genetic diagnosis (ACOG, NHLBI, RCOG), counselling during pregnancy (all four CPGs), transfusion or prophylactic exchange transfusion (ACOG, NICE, RCOG), fetal surveillance (ACOG, NHLBI, RCOG), and contraception (NHLBI, RCOG).

One Discrepancy was observed in the form of a lack of clearly articulated recommendations for vaccination status updated pre-pregnancy in three CPGs (ACOG, NHLBI, NICE) where it was addressed in the RCOG CPG only. PRISMA checklist was reported in Table 7.

Two CPGs (ACOG and RCOG) were more specific on pregnancy compared to the other two CPGs that contained general recommendations on SCD with smaller sections focused on pregnancy. Out of the two specific CPGs, RCOG consistently scored higher in all domains of our assessment. This systematic and objective assessment of the available CPGs is beneficial to support the decision to adopt or adapt CPGs in clinical practice. After reviewing these CPGs and given the appropriate rigor and consistently high scores with RCOG and its relevance clinically, we decided to adopt all the recommendations of this CPG in our clinical practice.

The findings of our study revealed that the CPG assessment was accurate. There was excellent/ very good inter-rater agreement between the four assessors who evaluated the eligible four CPGs using AGREE II. In our results, we were able to show that our proposed approach for quality assessment could be seen as a significant example of similar systematic reviews and assessments of CPGs.

Furthermore, our statistical analysis illustrates the practicability of the AGREE II instrument as a valuable tool in the critical appraisal of CPGs, without compromising quality. We trust in the experience of our raters who participated in the inter-observer agreement. Conceivably, inexperienced staff or non-professional reviewers would not have been able to have similar agreement on clinical decision features or characteristics in CPGs that could impact the judgement related to the provision of care to pregnant women with SCD.

In the first half of 2019 only, more than eight systematic critical appraisals of CPGs in obstetrics and gynecology have been published using the AGREE II instrument. These included high priority health topics like; induction of labor[32], planned caesarean section[33], recurrent pregnancy loss[34], packed red cells versus whole blood transfusion for severe pregnancy-related anemia and obstetric bleeding[35], gestational diabetes mellitus[36-38], and bladder pain syndrome/interstitial cystitis[39]. The studies mentioned above studies have identified several gaps in the included CPGs, including differences, discrepancies, lack of evidence-base, and inconsistencies in some clinical recommendations in addition to commonalities and similarities in other recommendations with future advice to improve these variabilities in CPGs.[32-39]

## Strengths and limitations

We identified several strengths in our study to share. Firstly, the appraisal conducted in this review was performed by an expert specialized clinical team of obstetricians and gynaecologists, internists, and hematologists guided by an expert CPG methodologist, which adds a layer of strength to the AGREE II assessment.

An additional implication for clinical practice is to encourage care providers for pregnant women with SCD to adopt principles of 'evidence-based' and 'eminence-based' healthcare together in their daily practice through continuous training and education on standards of high-quality CPG and their appraisal tools.[27-31]

Furthermore, the results of this review can be used as a basis for CPG development or adaptation projects for pregnant women with SCD. Furthermore, they highlight the importance of inclusion of the AGREE II criteria in the capacity building for clinicians to guide their identification and adoption of CPGs for use in their daily practice.

The study methodology has several strengths as well; (i) the use of an international, rigorously structured, and validated CPG appraisal tool: the AGREE II instrument, (ii) appraisal of each CPG by four raters including four clinical topic experts and a CPG methodologist, (iii) a comprehensive search within several databases, (iv) interrater differences were statistically assessed.

Our study also has several limitations. First, the AGREE II instrument has several updates and different versions. Some of the disadvantages of AGREE II have been addressed in the recently developed 'AGREE-REX' (Recommendation EXcellence) tool that addresses clinical credibility of the CPG recommendations. AGREE-REX has been validated and shared publicly on the wesbite.[26]

The selection of 70% as a cut-off point for standard domain ratings is another potential limitation as the original AGREE II does not mandate such a cut- off but similar studies have suggested so as well.[25]

Other limitations include, apart from those imposed by the AGREE II, the following; (i) English language CPGs may have resulted in the exclusion of relevant CPGs intended for use in non-English speaking healthcare settings; (ii) this review mainly focused on CPGs for management of pregnant women with SCD, due to its known burden and priority for maternity health, and did not evaluate other subcategories of the sickle cell as it was out of the scope of this study; (iii) The included CPGs belong to two different healthcare systems (i.e. US-based and UK-based)

## Conclusions

The AGREE II assessment of the four included SCD in pregnancy CPGs revealed methodological shortcomings in several domains. We recommend several areas for improvement for future CPGs, using the AGREE II criteria and the RCOG and NICE CPGs as models. The NICE 2016, RCOG 2018, followed by the NHLBI 2014 CPGs, showed the highest quality and were strongly recommended in the present evaluation. This critical appraisal highlights the importance of quality assessment of CPGs by clinicians to ensure the transparency and strength of the CPG development process according to international CPG standards and to support the provision of best practice for pregnant women with SCD. We recommend incorporating the AGREE II appraisal of CPGs in the capacity building of Obstetricians and Gynecologists and Hematologists.

## Conflict of interest

The authors have no competing interests to declare. All are staff of the King Saud University and its University Medical City.

## Summary of work done by the contributors

The contributors are expert researchers in the relevant fields of (i) evidence-based healthcare and clinical practice guidelines (YSA), (ii) haematology an Hemoglobinopathies (GME, OTK, and MFA), (iii) obstetrics and gynecology and maternal healthcare (YSS, and AMA), and (iv) public health and biostatistics (AME).

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**Figure legends**

**Figure 1**

**From:** Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org.

**Figure 2**

**Abbreviations:** ACOG: American College of Obstetricians and Gynecologists; AGREE: Appraisal of Guidelines for Research and Evaluation, CPG: clinical practice guideline or guidance; NICE: National Institute of Health and Care Excellence; NHLBI: National Institutes of Health, National Heart, Lung, and Blood Institute; and RCOG: Royal College of Obstetricians and Gynaecologists, SCD: Sickle cell disease.

**Figure 3Abbreviations** : ACOG: American College of Obstetricians and Gynecologists; AGREE: Appraisal of Guidelines for Research and Evaluation, CPG: clinical practice guideline or guidance; D: AGREE II Domain, NICE: National Institute of Health and Care Excellence; NHLBI: National Institutes of Health, National Heart, Lung, and Blood Institute; OA1: AGREE II Overall assessment 1, Q: AGREE II Question (or Item), RCOG: Royal College of Obstetricians and Gynaecologists, and SCD: Sickle cell disease.

**Tables**

**Table 1. Interpretation of the strength of agreement according to K value.**

| Value of K | Strength of agreement |
|---|---|
| $< 0.20$ | Poor |
| 0.21 - 0.30 | Fair |
| 0.31 - 0.40 | Moderate |
| 0.41 - 0.60 | Good |
| 0.61 - 0.80 | Very good |
| 0.81 – 1.00 | Excellent |

**Table 2. Characteristics of the included SCD in pregnancy CPGs**

| Title | Year of publication | Country | Level of development | Organization (short name) | Total number of references |
|---|---|---|---|---|---|
| **ACOG Practice Bulletin Clinical Management Guidelines for Obstetrician-Gynecologists, Number 78, January 2007 Hemoglobinopathies in Pregnancy** [20] | 2007 (Reaffirmed 2018) | United States | National | American College of Obstetricians and Gynecologists (ACOG) | 26 (one NCSR) |
| **Sickle cell disease: managing acute painful episodes in hospital. NICE Clinical guideline 143** [21] | 2012 (minor update in 2016) | United Kingdom | National | National Institute of Health and Care Excellence (NICE) | 97 (one NCSR) (reviewed and excluded NCSR and CSRs were not counted) |
| **Management of Sickle Cell Disease in Pregnancy (Green-top Guideline No. 61). Royal College of Obstetricians and Gynaecologists** [22] | 2011 (updated 2018) | United Kingdom | National | Royal College of Obstetricians and Gynaecologists (RCOG) | 80 (one NCSR, 5 CSR) |
| **Evidence-Based Management of Sickle Cell Disease: Expert Panel Report (EPR), 2014** [23] | 2014 (update) | United States | National | US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute (NHLBI) | 428 (5 NCSR, one CSR) |

**Abbreviations:** CPG: clinical practice guideline; CSR: Cochrane systematic review; NCSR: Non-Cochrane systematic review

**Table 3. AGREE II standardized domain scores**

| CPGs/ AGREE II Domains-standardized scores (%) | ACOG 2018[20] | NICE 2016[21] | RCOG 2018[22] | NHLBI 2014[23] |
|---|---|---|---|---|
| **Domain 1. Scope and Purpose** **Items 1-3:** Objectives; Health question(s); Population (patients, public, etc.). | 76 | 93 | 89 | 78 |
| **Domain 2. Stakeholder Involvement** **Items 4-6:** Group Membership; Target population preferences and views; Target users. | 33 | 85 | 76 | 55 |
| **Domain 3. Rigour of development** **Items 7-14:** Search methods; Evidence selection criteria; Strengths and limitations of the evidence; Formulation of recommendations; Consideration of benefits and harms; Link between recommendations and evidence; External review; Updating procedure. | **41** | 90 | **73** | **35** |
| **Domain 4. Clarity and presentation** **Items 15-17:** Specific and unambiguous recommendations; Management options; Identifiable key recommendations | 63 | 89 | 83 | 94 |

| CPGs/ AGREE II Domains-standardized scores (%) | ACOG 2018[20] | NICE 2016[21] | RCOG 2018[22] | NHLBI 2014[23] |
|---|---|---|---|---|
| **Domain 5. Applicability Items 18-21:** Facilitators and barriers to application; Implementation advice/ tools; Resource implications; Monitoring/ auditing criteria | **24** | 90 | **46** | **35** |
| **Domain 6. Editorial independence Items 22, 23:** Funding body; Competing interests | 19 | 71 | 77 | 39 |
| **Overall Assessment 1** (Overall quality) | 46 | 83 | 79 | 53 |
| **Overall Assessment 2** (Recommend the CPG for use) | Yes-1, Yes with modifications-2, No-1 | Yes-1, Yes with modifications-3, No-0 | Yes-2, Yes with modifications-2, No-0 | Yes-3, Yes with modifications-1, No-0 |

**Abbreviations:** ACOG: American College of Obstetricians and Gynecologists; AGREE II: Appraisal of Guidelines for Research and Evaluation II; CPG: clinical practice guideline or guidance; NICE: National Institute of Health and Care Excellence; NHLBI: National Institutes of Health, National Heart, Lung, and Blood Institute; and RCOG: Royal College of Obstetricians and Gynaecologists.

| **Table 4. Summary of the reviewers' comments organized by the AGREE II standardized domains on management of SCD in pregnancy CPGs from the ACOG, NHLBI, NICE, and RCOG[20-23*]** | **Table 4. Summary of the reviewers' comments organized by the AGREE II standardized domains on management of SCD in pregnancy CPGs from the ACOG, NHLBI, NICE, and RCOG[20-23*]** | **Table 4. Summary of the reviewers' comments organized by the AGREE II standardized domains on management of SCD in pregnancy CPGs from the ACOG, NHLBI, NICE, and RCOG[20-23*]** |
|---|---|---|
| **AGREE II Domain** | **Strengths** | **Limitations** |
| **Domain 1. Scope and Purpose** | Objectives, purpose, health intent, clinical questions, patient population were clearly mentioned in the CPG full document or the website using the PICO model (NICE, NHLBI, RCOG). | Target users were general rather than specific (ACOG) |

| Table 4. Summary of the reviewers' comments organized by the AGREE II standardized domains on management of SCD in pregnancy CPGs from the ACOG, NHLBI, NICE, and RCOG[20-23*] | Table 4. Summary of the reviewers' comments organized by the AGREE II standardized domains on management of SCD in pregnancy CPGs from the ACOG, NHLBI, NICE, and RCOG[20-23*] | Table 4. Summary of the reviewers' comments organized by the AGREE II standardized domains on management of SCD in pregnancy CPGs from the ACOG, NHLBI, NICE, and RCOG[20-23*] |
|---|---|---|
| **Domain 2. Stakeholder Involvement** | GDG members' names, specialties, institutions, and geographical locations were clearly mentioned and easy to find. GDG included methodologist(s) (NICE, RCOG). GDG included members from relevant professional groups including patient representatives (NICE) | GDG disciplines and roles were not clearly mentioned (ACOG). GDG was missing some key disciplines (e.g. pharmacists and nurses) (RCOG)002E Lack of adequate and clear descriptions of patient participation or preferences and target users (ACOG, NHLBI). |
| **Domain 3. Rigour of development** | Detailed evidence search keywords were mentioned (NICE, RCOG). The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to assess the quality of evidence was utilized (NICE, NHLBI) Recommendations include health benefits, harms, and side effects of recommendations with or without a discussion of their trade-offs (NICE, NHLBI). All recommendations were linked to their relevant primary source of evidence (NICE, NHLBI, RCOG). Lists and processes of external review were clearly reported and easy to find (NICE, NHLBI, RCOG). Updating was clearly mentioned (NICE, RCOG). | Lack of detailed search strategy (ACOG). Strengths and limitations of the body of evidence (evidence tables) were not clearly reported (ACOG). Lack of detailed process for formulation of the recommendations, and discussion of trade-off between harms and benefits (ACOG, RCOG). Details and methods of the external review process and outcomes were not clearly reported (ACOG). Review and update process was not reported (ACOG, NHLBI) |
| **Domain 4. Clarity and presentation** | This domain was well-addressed in most included CPGs, where key recommendations were specific, unambiguous, and easily identifiable in all CPGs (NICE, NHLBI, RCOG). | Management of SCD Crisis in different pregnancy trimesters and abnormal fetal surveillance management were not highlighted (ACOG). |

| Table 4. Summary of the reviewers' comments organized by the AGREE II standardized domains on management of SCD in pregnancy CPGs from the ACOG, NHLBI, NICE, and RCOG[20-23*] | Table 4. Summary of the reviewers' comments organized by the AGREE II standardized domains on management of SCD in pregnancy CPGs from the ACOG, NHLBI, NICE, and RCOG[20-23*] | Table 4. Summary of the reviewers' comments organized by the AGREE II standardized domains on management of SCD in pregnancy CPGs from the ACOG, NHLBI, NICE, and RCOG[20-23*] |
|---|---|---|
| **Domain 5. Applicability** | Some facilitators and barriers to implementations and clinical governance issues were discussed (NHLBI, NICE, RCOG). A package of CPG Implementation tools were provided like educational tools (NICE), protocols (NHLBI), summary document (NHLBI, NICE, RCOG), patient information (NHLBI, NICE), clinical algorithm or pathway (NHLBI, NICE), baseline assessment sheet (NICE), Mobile App (RCOG). Quality standards, measures, indicators, and/ or clinical audit criteria were provided (NICE, RCOG). A formal economic analysis was conducted (NICE). | Facilitators and barriers to implementations were not explicitly mentioned (ACOG). Implementation tools were not provided (ACOG). Quality measures or key performance indicators were not provided (ACOG, NHLBI). No formal economic analysis was conducted (ACOG, NHLBI, and RCOG). |
| **Domain 6. Editorial independence** | Funding with or without an influence statement were mentioned (NICE, NHLBI, RCOG). DCOI statements were clearly provided (NICE, NHLBI, RCOG). | Funding and influence statements were not clearly reported (ACOG, NHLBI). No DCOI statements were provided (ACOG). |

**Abbreviations:** ACOG: American College of Obstetricians and Gynecologists; AGREE II: Appraisal of Guidelines for Research and Evaluation II; CPG: clinical practice guideline or guidance; DCOI: declaration of conflict of interests; NICE: National Institute of Health and Care Excellence; NHLBI: National Institutes of Health, National Heart, Lung, and Blood Institute; PICO: patient population -intervention(s)-comparison(s)-outcome(s); and RCOG: Royal College of Obstetricians and Gynaecologists. *Comments specific to certain CPG(s) were indicated by parentheses.

| **Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG*** | **Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG*** | **Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG*** | **Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG*** | **Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG*** |
|---|---|---|---|---|
| **CPGs/ Recommendations** | **ACOG** [20] | **NHLBI** [21] | **NICE** [22] | **RCOG** [23] |
| **Preconception care** | **Preconception care** | **Preconception care** | **Preconception care** | **Preconception care** |
| **Genetic screening** | Individuals of African, Southeast Asian, and Mediterranean descent are at increased risk for being carriers of hemoglobinopathies and should be offered carrier screening and, if both parents are determined to be carriers, genetic counselling. | If the partner of a man or woman with SCD has unknown SCD or thalassemia status, refer the partner for hemoglobinopathy screening. After testing, refer couples who are at risk for having a potentially affected fetus and neonate for genetic counseling. | Not Mentioned | Women and men with SCD should be encouraged to have the hemoglobinopathy status of their partner determined before they embark on pregnancy. If identified as an 'at risk couple', as per National Screening Committee guidance, they should receive counselling and advice about reproductive options. |
| **Penicillin prophylaxis** | Not mentioned | Mentioned for the pediatric but not for the pregnant women population. | Not mentioned | Penicillin prophylaxis or the equivalent should be prescribed |

| Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* |
|---|---|---|---|---|
| **Vaccination status updated pre-pregnancy** | Not Mentioned | Mentioned in general for the adult population but not specifically for pregnant women | Not Mentioned | Women should be given *H. influenza* type b and the conjugated meningococcal C Vaccine as a single dose if they have not received it as part of primary vaccination. The pneumococcal vaccine should be given every 5 years. Hepatitis B vaccination is recommended and the woman's immune status should be determined preconceptually. Women with SCD should be advised to receive the influenza and 'swine flu' vaccine annually. |

| **Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG*** | **Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG*** | **Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG*** | **Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG*** | **Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG*** |
|---|---|---|---|---|
| **Vitamin supplementation** | Pregnant patients with SCD need increased prenatal folic acid supplementation. The standard 1 mg of folate in prenatal vitamins is not adequate for patients with hemoglobinopathies; 4 mg per day of folic acid should be prescribed because of the continual turnover of red blood cells. | Folic acid supplementation should be used whenever considering or at risk of pregnancy to prevent neural tube defects. | Not Mentioned | Folic acid (5 mg) should be given once daily both preconceptually and throughout pregnancy. |
| **Medication review** | Hydroxyurea has been shown to reduce the frequency of painful crises in non-pregnant patients with severe SCD. However, the use of hydroxyurea is not recommended during pregnancy because it is teratogenic. | In females who are pregnant or breastfeeding, discontinue hydroxyurea therapy. | Not Mentioned | Hydroxycarbamide (hydroxyurea) should be stopped at least 3 months before conception. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be stopped before conception. |
| **Antenatal care** | **Antenatal care** | **Antenatal care** | **Antenatal care** | **Antenatal care** |

| Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* |
|---|---|---|---|---|
| **Antenatal hemoglobinopathy screening** | Not mentioned | Not mentioned | Not Mentioned. But a link to the 'NHS Sickle Cell and Thalassaemia Screening Programme' was provided. | If the woman has not been seen preconceptually, she should be offered partner testing. If the partner is a carrier, appropriate counselling should be offered as early as possible in pregnancy – ideally by 10 weeks of gestation – to allow the option of first-trimester diagnosis and termination if that is the woman's choice. |

| Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* |
|---|---|---|---|---|
| **Medications during pregnancy** | Not mentioned | Not clearly mentioned for women during pregnancy. | Mentioned under research recommendations | If women have not undergone a pre-conceptual review, they should be advised to take daily folic acid and prophylactic antibiotics (if not contraindicated). Drugs that are unsafe in pregnancy should be stopped immediately. Iron supplementation should be given only if there is laboratory evidence of iron deficiency. Women with SCD should be considered for low-dose aspirin 75 mg once daily from 12 weeks of gestation in an effort to reduce the risk of developing pre-eclampsia. Women with SCD should be advised to receive prophylactic low-molecular-weight heparin during antenatal hospital admissions. |

| Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* |
|---|---|---|---|---|
| **Blood transfusion or prophylactic exchange transfusion for pregnancies** | Recommended just to keep of Hb S to approximately 40% While simultaneously raising the total haemoglobin concentration to about 10 g/dL. | Not Mentioned | Not Mentioned | Routine prophylactic transfusion is not recommended during pregnancy for women with SCD. If acute exchange transfusion is required for the treatment of a sickle complication, it may be appropriate to continue the transfusion regimen for the remainder of the pregnancy. Blood should be matched for an extended phenotype including full rhesus typing (C, D and E) as well as Kell typing. Blood used for transfusion in pregnancy should be cytomegalovirus negative. |

| Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* |
|---|---|---|---|---|
| **Ultrasound Scanning and fetal surveillance during pregnancy** | Pregnancies in women with sickle cell disease are at increased risk for spontaneous abortion, preterm labor, IUGR, and stillbirth. For this reason, a plan for serial ultrasound examinations and antepartum fetal testing is reasonable. | Fetal surveillance, which includes growth ultrasounds and antepartum testing (non-stress tests, biophysical profiles, and contraction stress tests), may lead to planned early delivery and can reduce but not eliminate risks (not mentioned as a recommendation). | Not mentioned | Women should be offered a viability scan at 7–9 weeks of gestation. Women should be offered the routine first-trimester scan (11–14 weeks of gestation) and a detailed anomaly scan at 20 weeks of gestation. In addition, women should be offered serial fetal biometry scans (growth scans) every 4 weeks from 24 weeks of gestation. |

| Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* |
|---|---|---|---|---|
| **Acute painful crisis** | Major complications (e.g., worsening anemia; intrapartum complications such as hemorrhage, septicemia, and cesarean delivery; painful crisis; and chest syndrome) may require intervention with an exchange transfusion (not mentioned as a recommendation). Painful crises in pregnancy as well as in the non-pregnant patient are managed with rapid assessment of the level of pain and prompt administration of analgesia. | Not clearly mentioned for women during pregnancy. | For pregnant women with an acute painful sickle cell episode, seek advice from the obstetrics team and refer when indicated. Offer all patients regular paracetamol and NSAIDs (non-steroidal anti-inflammatory drugs) by a suitable administration route, in addition to an opioid, unless contraindicated (Not clearly mentioned for women during pregnancy). The use of NSAIDs should be avoided during pregnancy, unless the potential benefits outweigh the risks. NSAIDs should be avoided for treating an acute painful sickle cell episode in women in the third trimester. See the 'British National Formulary' for details of contraindications. | Women with SCD who become unwell should have sickle cell crisis excluded as a matter of urgency. Pregnant women presenting with acute painful crisis should be rapidly assessed by the multidisciplinary team and appropriate analgesia should be administered. Pethidine should not be used because of the associated risk of seizures. Women admitted with sickle cell crisis should be looked after by the multidisciplinary team, involving obstetricians, midwives, hematologists and anaesthetists. The requirement for fluids and oxygen should be assessed, and fluids and oxygen administered if required. Thrombo-prophylaxis should be given to women admitted to hospital with acute painful crisis |

| Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* |
|---|---|---|---|---|
| **Intrapartum care** | **Intrapartum care** | **Intrapartum care** | **Intrapartum care** | **Intrapartum care** |
| **Timing and mode of delivery** | Not mentioned | Not mentioned | Not mentioned | Pregnant women with SCD who have a normally growing fetus should be offered elective birth through induction of labour, or by elective caesarean section if indicated, after 38+0 weeks of gestation. SCD should not in itself be considered a contraindication to attempting vaginal delivery or vaginal birth after caesarean section. Blood should be cross-matched for delivery if there are atypical antibodies present (since this may delay the availability of blood), otherwise a 'group and save' will suffice. In women who have hip replacements (because of avascular necrosis) it is important to discuss suitable positions for delivery. |

| Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* |
|---|---|---|---|---|
| **Optimal mode of analgesia and anaesthesia** | Not mentioned (analgesia mentioned with painful crisis). | Not clearly mentioned for women during pregnancy. | Not mentioned | Women with SCD should be offered anaesthetic assessment in the third trimester of pregnancy. Avoid the use of pethidine, but other opiates can be used. Regional analgesia is recommended for caesarean section. |
| **Postpartum care** | **Postpartum care** | **Postpartum care** | **Postpartum care** | **Postpartum care** |
| **Neonatal screening** | Not mentioned | Not mentioned | Not mentioned | In pregnant women where the baby is at high risk of SCD (i.e. the partner is a carrier or affected), early testing for SCD should be offered. Capillary samples should be sent to laboratories where there is experience in the routine analysis of SCD in newborn samples. This will usually be at a regional centre. |

| Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* | Table 5. Summary of key recommendations of the four eligible SCD in pregnancy CPGs from ACOG, NHLBI, NICE, and RCOG* |
|---|---|---|---|---|
| **VTE prophylaxis** | Not Mentioned | Not clearly mentioned for women during pregnancy. | Not mentioned | Low-molecular-weight heparin should be administered while in hospital and 7 days post-discharge following vaginal delivery or for a period of 6 weeks following caesarean section. |
| **Contraception** | Not Mentioned | Progestin-only contraceptives (pills, injections, and implants), levonorgestrel IUDs, and barrier methods have no restrictions or concerns for use in women with SCD. If the benefits are considered to outweigh the risks, combined hormonal contraceptives (pills, patches, and rings) may be used in women with SCD. | Not Mentioned | Progestogen-containing contraceptives such as the progesterone only pill, injectable contraceptives and the levonorgestrel intrauterine system are safe and effective in SCD. Estrogen-containing contraceptives should be used as second-line agents. Barrier methods are as safe and effective in women with SCD as in the general population. |

**Abbreviations:** ACOG: American College of Obstetricians and Gynecologists; CPG: clinical practice guideline or guidance; DCOI: declaration of conflict of interests; NICE: National Institute of Health and Care Excellence; NHLBI: National Institutes of Health, National Heart, Lung, and Blood Institute; PGD: Preimplantation genetic diagnosis; and RCOG: Royal College of Obstetricians and Gynaecologists.

**Table 6. Classification of the strength of agreement among the four raters against the four SCD in pregnancy clinical practice guidelines**

| | Poor | Fair | Good | Very good | Excellent | Overall assessment 1 |
|---|---|---|---|---|---|---|
| **RCOG** | 0 | 0 | 15 | 9 | 0 | Good |
| **NICE** | 0 | 0 | 16 | 7 | 1 | Good |
| **ACOG** | 2 | 0 | 16 | 5 | 1 | Good |
| **NHLBI** | 0 | 0 | 15 | 9 | 0 | Good |

**Table 7. PRISMA Statement Checklist**

| Section/topic | # | Checklist item |
|---|---|---|
| **RESULTS** | **RESULTS** | **RESULTS** |
| **Study selection** | 17 | Give numbers of studies screened, assessed for eligibility, and included |
| **Study characteristics** | 18 | For each study, present characteristics for which data were extracted |
| **Risk of bias within studies** | 19 | Present data on risk of bias of each study and, if available, any outco |
| **Results of individual studies** | 20 | For all outcomes considered (benefits or harms), present, for each stu |
| **Synthesis of results** | 21 | Present results of each meta-analysis done, including confidence inter |
| **Risk of bias across studies** | 22 | Present results of any assessment of risk of bias across studies (see Ite |
| **Additional analysis** | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgrou |
| **DISCUSSION** | **DISCUSSION** | **DISCUSSION** |
| **Summary of evidence** | 24 | Summarize the main findings including the strength of evidence for ea |
| **Limitations** | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and |
| **Conclusions** | 26 | Provide a general interpretation of the results in the context of other |
| **FUNDING** | **FUNDING** | **FUNDING** |
| **Funding** | 27 | Describe sources of funding for the systematic review and other suppo |

*Table 7. PRISMA statement Checklist (continued)*

| Section/topic | # | Checklist item |
|---|---|---|
| **RESULTS** | **RESULTS** | **RESULTS** |
| **Study selection** | 17 | Give numbers of studies screened, assessed for eligibility, and included |
| **Study characteristics** | 18 | For each study, present characteristics for which data were extracted |
| **Risk of bias within studies** | 19 | Present data on risk of bias of each study and, if available, any outco |
| **Results of individual studies** | 20 | For all outcomes considered (benefits or harms), present, for each stu |
| **Synthesis of results** | 21 | Present results of each meta-analysis done, including confidence inter |
| **Risk of bias across studies** | 22 | Present results of any assessment of risk of bias across studies (see Ite |
| **Additional analysis** | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgrou |
| **DISCUSSION** | **DISCUSSION** | **DISCUSSION** |
| **Summary of evidence** | 24 | Summarize the main findings including the strength of evidence for ea |
| **Limitations** | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and |
| **Conclusions** | 26 | Provide a general interpretation of the results in the context of other |
| **FUNDING** | **FUNDING** | **FUNDING** |
| **Funding** | 27 | Describe sources of funding for the systematic review and other suppo |

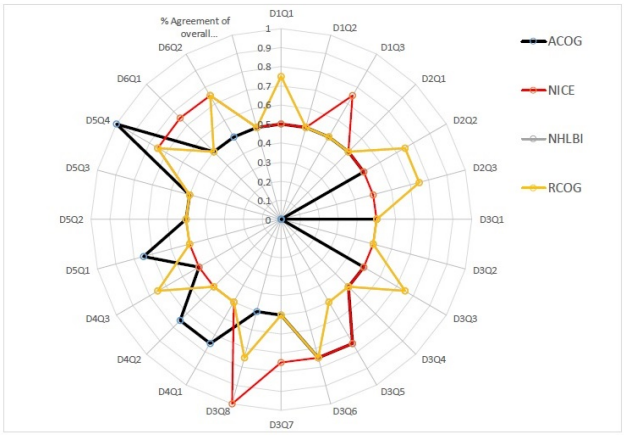


**Figure 3: Using a radar chart to map the AGREE II 23-questions/items, 6-domains, and the first overall assessment (OA1) for the SCD pregnancy CPGs**

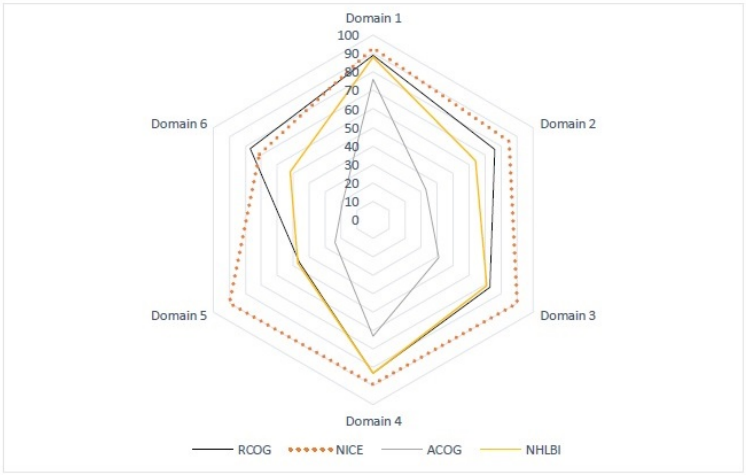


**Figure 2: Radar map of the AGREE II final standardized domain scores for each included SCD pregnancy CPG.**

**Figure 1. PRISMA 2009 Flow Diagram**
**Systematically searching and selecting the clinical practice guidelines for management of pregnant women with sickle cell disease**