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Research Article

Quality Appraisal of the British Society of Haematology Guideline for the Management of Sickle Cell Disease in Pregnancy Using the AGREE II, AGREE-REX, and CheckUp Guideline Tools

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Abstract

Introduction: In 2021, the British Society for Haematology (BSH) updated the Royal College of Obstetricians and Gynaecologists (RCOG) Clinical Practice Guideline (CPG) on the management of pregnant women with sickle cell disease including several updated recommendations.

Aim of the Study: The aim of this study was to appraise the quality of the updated BSH CPG.

Methods: We used three CPG appraisal tools including the AGREE II, AGREE-REX, and CheckUp tools to evaluate the quality of the BSH CPG from different aspects.

Results: The AGREE II appraisal showed high scores in the six standardized domains and the AGREE-REX appraisal received high scores in its three domains. The group appraisal using both tools recommended using the BSH in practice. The updated BSH CPG complied with 81% of the CheckUp Tool items and it covered all options of care for women.

Conclusion: The updated BSH CPG for sickle cell disease in pregnancy was identified as a high-quality evidence-based CPG using three CPG appraisal tools (AGREE II, AGREE-REX and CheckUp).

Keywords: *Sickle Cell Disease (SCD); AGREE II; AGREE-REX; CheckUp*

Introduction

Pregnant women with sickle cell disease (SCD) remain at risk of adverse maternal and perinatal outcomes despite the current improvement in their healthcare provision. Maternal and obstetric complications include pain, pulmonary events, infections, thromboembolism, pre-eclampsia, and maternal mortality. Neonatal complications include: fetal (or intrauterine) growth restriction, premature birth, and stillbirth [1,2].

The situation is not different in Saudi Arabian pregnant women with SCD [3,4].

In 2009, a guideline adaptation and implementation program was launched in the University Hospitals and Medical City of King Saud University (KSUMC) that included reviewing, appraising, adapting, implementing, and evaluating evidence-based clinical practice guidelines with aim of improving the healthcare quality, patient safety, and patient outcomes [5,6].

One of the high-priority health topics that have been identified by the KSUMC Oncology Center for guideline adaptation and implementation was the management of SCD in pregnant women. A guideline adaptation group (GAG) was formulated of expert consultant internists, hematologists, obstetricians and gynecologists, clinical pharmacists, and laboratory medicine guided by an expert guideline methodologist [7].

The GAG conducted a systematic review of CPGs for SCD in pregnancy and a critical appraisal of the included CPGs using the Appraisal of Guidelines for Research and Evaluation (AGREE) II Instrument that is considered by the guideline research community as the gold standard for quality assessment of any CPG [8-11]. The findings of this review showed that the first edition of the Royal College of Obstetricians and Gynaecologists Green-Top Guideline was one of the high-quality guidelines according to the AGREE II assessment criteria where its third Domain, Rigour of Development, received a standardized domain score of 73% [8-12].

During the assessment of currency of the RCOG CPG the GAG noticed the statement posted in the official RCOG website that it will be only valid till the publication of the updated CPG that will be taken over by the British Society for Haematology (BSH) [11].

The updated CPG was finally released by the BSH in 19th of August 2021 and to the best of our knowledge, no previous study appraised its quality.

Objective of the Study

The objective of the study is to assess the quality of the BSH CPG for the management of SCD in pregnancy by using three different CPG appraisal tools: (i) the AGREE II Instrument (to assess its methodological quality), (ii) the AGREE-REX or Recommendation EXcellence Tool (to assess its clinical credibility and implementability), in addition to (iii) the Checklist for the Reporting of Updated Guidelines (CheckUp) (to assess the completeness of reporting in updated guidelines) [9,10,13-15].

Methods

The authors comprised a multidisciplinary group including all stakeholders that provide healthcare for women with SCD or that conduct research to improve their evidence-based healthcare quality and safety (e.g. a hematologist, obstetrician and gynecologist, clinical pharmacist, nurse, and guideline methodologist). The AGREE Enterprise has developed a set of tools to support developing, reporting, and evaluating CPGs and health system guidance. Three tools have been chosen to be used in the assessment of the BSH CPG in our study including the following.

The appraisal of guidelines for research and evaluation II instrument (AGREE II)

The AGREE II instrument (www.agreetrust.org) consists of 23 items organized in six domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence (Table 1) [11,16]. A Likert scale, from 1 to 7,

is used to rate each item. The AGREE II evaluation was directed by its online version, "My AGREE PLUS," which supports the establishment of a CPG "appraisal group" for each CPG that accumulates and calculates item scores into domain ratings, as well as comments [11,16]. The study included five AGREE II raters that had relevant clinical and methodological expertise (GE, YA, FA, AH and MA). Large differences in assessors' ratings for items or questions (≥ 3) were handled by requesting the owners of the outlying scores to re-assess the questions after conversations with the group. Using My AGREE PLUS, the standardized AGREE domain scores or ratings (percent) were automatically calculated. Each AGREE standardized domain score or rating was given a 60% cut-off point to determine the CPG quality.

Domains	Items
1. Scope and Purpose	1. Objectives 2. Health question(s) 3. Population (patients, public, etc.).
2. Stakeholder Involvement	4. Group Membership 5. Target population preferences and views 6. Target users.
3. Rigour of development	7. Search methods 8. Evidence selection criteria 9. Strengths and limitations of the evidence 10. Formulation of recommendations 11. Consideration of benefits and harms 12. Link between recommendations and evidence 13. External review 14. Updating procedure.
4. Clarity and presentation	15. Specific and unambiguous recommendations 16. Management options 17. Identifiable key recommendations.
5. Applicability	18. Facilitators and barriers to application 19. Implementation advice/ tools 20. Resource implications 21. Monitoring/ auditing criteria.
6. Editorial independence	22. Funding body 23. Competing interests.
Overall Assessment 1	Overall quality of the CPG
Overall Assessment 2	Recommending the CPG for use in practice

Table 1: *The domains and items of the AGREE II Instrument*.*

**Each of the 6 domains and the first overall assessment is represented independently by a percentage (%). The second overall assessment is represented by the number of AGREE II assessors who answered: Yes, Yes with modifications, or No.*

The appraisal of guidelines research and evaluation-recommendations excellence tool (AGREE-REX)

The AGREE-REX (www.agreetrust.org) consists of 11 items organized in three domains: Evidence justification, Clinical applicability justification, Values justification, Feasibility considerations (Table 2) [11,16-18]. A Likert scale, from 1 to 7, is used to rate each item. Five appraisers have chosen using the consensus approach to reach agreement about AGREE-REX item scores. There is currently no online version for the AGREE-REX unlike the AGREE II and the raters used the calculation equation provided by the AGREE-REX Tool [17,18]. A free online calculator (https://www.calculator.net/) was used to calculate the arithmetic mean (consensus item score) for each Item.

Domains	Items
1. Clinical applicability	1. Evidence. 2. Applicability to Target Users. 3. Applicability to Patients/ Populations.
2. Values and Preferences	4. Values and Preferences of Target Users. 5. Values and Preferences of Patients/ Populations. 6. Values and Preferences of Policy/ Decision-Makers. 7. Values and Preferences of Guideline Developers
3. Implementability	8. Purpose. 9. Local Application and Adoption.

Table 2: *The domains and items of the AGREE-REX instrument.*

Scores for each item or domain were computed using the guidance provided in the AGREE II and AGREE-REX instrument user manuals.

The checklist for the reporting of updated guidelines (CheckUp)

The CheckUp could be used to evaluate the completeness of updated recommendation reporting in any updated CPG and to provide advice to guideliners on reporting criteria [15,19]. It consists of 16 items grouped into three categories: Firstly, presentation (for example, CPG sections and recommendations), Secondly, editorial independence (for example, the CPG group and financing), and thirdly, methodology (for example, search strategy and evidence synthesis) [15,19].

Results

Quality appraisal of the BSH CPG

The AGREE II appraisal results

Five raters appraised the BSH CPG using the AGREE II and discussed any discrepancies at the end. The BSH develops CPGs based on the AGREE II criteria and follows the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) Method. The AGREE II assessment revealed the following ratings.

AGREE II domain 1: Scope and purpose

Domain 1 scored 83% where the objective of the CPG was specifically described, health questions are part of the BSH methodology but they were not clearly described in the CPG article, the included and excluded patient populations were clearly in the introduction.

AGREE II domain 2: Stakeholder involvement

Domain 2 scored 79%. The guideline development group (GDG) was formulated by the BSH General Haematology Task Force members and the BSH Obstetric Special Interest Group which included experts in obstetrics and gynecology, women's health, hematology, and pub-

lic health. But it was not clear whether the GDG included nurses or clinical pharmacists. Despite the fact that involving patient representatives in the GDG is part of the BSH CPG methodology, it was not clear in this CPG article's author of GDG.

The CPG recommended that senior obstetricians, hematologists, obstetric anesthetists, obstetric physicians, specialist nurses and midwives should constitute a multidisciplinary integrated team. Pharmacists were not mentioned despite the CPG includes pharmacological therapy.

AGREE II domain 3: Rigor of development

The CPG received a good score (90%) in the most important domain that appraises the main components of the CPG: the evidence-based, evidence-to-recommendations, and the recommendations' writing. BSH provides a separate online CPG development methodology detailed document in its official website and linked to the CPG article (https://b-s-h.org.uk/media/19927/bsh-guidance-development-process-july-2021.pdf).

The literature review and search details were provided in the CPG article.

AGREE II domain 4: Clarity of presentation

Domain 4 scored 86% emphasizing that the recommendation statements are clear and specific, and presenting the different options of management of SCD in pregnancy including a set of key recommendations.

AGREE II domain 5: applicability

Domain 5 scored 58% that reflected the identification of some barriers were identified like non-invasive testing, genetic screening. Two CPGI Tools were provided in the CPG article including a tool for preconception review of chronic sickle complications and another tool for specific antenatal care for women with SCD. Several practical tools were provided on the BSH official website like hematology images (https://b-s-h.org.uk/education/haematology-images/) and educational resources but were not linked to the CPG article. BSH mentioned that it was beyond its scope to conduct a cost-effectiveness analysis for each recommendation, and it believes that it is up to institutions to evaluate the guidance produced and weigh the risks of implementing or not in the context of their own priority areas and communities.

Despite mentioning the importance of having CPG-related audit tools in the BSH methodology document and having a Hematology Audit template and action plan made available as a downloadable fillable Microsoft Word file from the CPG official website (https://b-s-h.org.uk/guidelines/guidelines/gl-management-of-sickle-cell-disease-in-pregnancy/), this was not linked to the CPG article and no further details were provided on its usability or recommended frequency of measurement.

AGREE II domain 6: Editorial independence

The CPG revealed a good rating (73%) as it reported its funding that involved only the travel expenses of the members of writing groups, task forces, and the BSH executives. It also reported the declaration of conflicts of interest for all members and the process was explicitly described in the BSH methodology document.

AGREE II overall assessment

The first assessment of the overall quality of the CPG showed a score of 88% that reflects the high scores of the 6 AGREE II domain scores.

AGREE II: Recommending the ASD CPGs for use in practice

All of the four raters agreed on recommending the BSH CPG for their colleagues to use in their daily practice based on the AGREE II domain scores where the answers were: Yes (n = 4), Yes with modifications (n = 0), and No (n = 0).

The AGREE-REX appraisal results

The reviewers decided to apply the AGREE-REX to all of the BSH CPG's recommendations as they believed that the quality of the BSH recommendations is consistent based on the AGREE II assessment in addition all these recommendations were being considered for adoption, adaptation, or implementation (Table 3). We included the additional optional second evaluation statement for each of the nine AGREE-REX items that appraises the appropriateness or suitability of the BSH CPG recommendations to the specific healthcare context at KSUMC. Furthermore, the reviewers conducting two meetings and applied the AGREE-REX appraisers' consensus scores [18].

Domains (Score)	Items		Consensus AGREE-REX Item Scores										
			A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	Mean
D1. Clinical applicability (86%)	1. Evidence.	Quality Assessment	6	6	6	6	6	5	5	5	5	5	5.5
		Suitability for use	6	6	6	6	6	6	6	6	6	6	6
	2. Applicability to Target Users.	Quality Assessment	7	7	7	7	7	7	7	7	7	7	7
		Suitability for use	6	6	6	6	6	6	6	6	6	6	6
	3. Applicability to Patients/ Populations.	Quality Assessment	5	5	5	5	5	5	5	5	5	5	5
		Suitability for use	6	6	6	6	6	6	6	6	6	6	6
D2. Values and Preferences (85%)	4. Values and Preferences of Target Users.	Quality Assessment	6	6	6	6	6	6	6	6	6	6	6
		Suitability for use	7	7	7	7	7	7	7	7	7	7	7
	5. Values and Preferences of Patients/ Populations.	Quality Assessment	5	5	5	5	5	5	5	5	5	5	5
		Suitability for use	5	5	5	5	5	5	5	5	5	5	5
	6. Values and Preferences of Policy/ Decision-Makers.	Quality Assessment	7	7	7	7	7	7	7	7	7	7	7
		Suitability for use	6	6	6	6	6	6	6	6	6	6	6
	7. Values and Preferences of Guideline Developers	Quality Assessment	7	7	7	7	7	6	6	6	6	6	6.5
		Suitability for use	6	6	6	6	6	7	7	7	7	7	6.5
D3. Implementability (92%)	8. Purpose	Quality Assessment	7	7	7	7	7	7	7	7	7	7	7
		Suitability for use	7	7	7	7	7	7	7	7	7	7	7
	9. Local Application and Adoption.	Quality Assessment	6	6	6	6	6	6	6	6	6	6	6
		Suitability for use	5	5	5	5	5	5	5	5	5	5	5
Overall assessment of the whole BSH CPG	We would recommend these CPG recommendations for use in the appropriate context.		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	We would recommend these CPG recommendations for use in our context		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table 3: *The AGREE-REX item and domain scores of the BSH CPG for SCD in pregnant women.*

Abbreviations: AGREE-REX: Appraisal of Guidelines for Research and Evaluation-Recommendation Excellence Instrument; BSH: British Society for Haematology; CPG: Clinical Practice Guidelines; D: Domain; SCD: Sickle Cell Disease.

AGREE-REX domain 1. Clinical applicability

This domain assesses whether the guideline is evidence-based (i.e. based on a thorough review and assessment of potential bias) as well as the degree to which the recommendations are applicable to the practice context and patients of the guideline's target users. BSH developed a CPG with a percentage value of 86%.

AGREE-REX domain 2. Values and preferences

This domain consists of four distinct items that refer to the relative value that target users, patients, policy/decision-makers, and guideline developers put on the outcomes of interest. Their values and preferences are important in the development of guidelines because they influence whether recommendations are acceptable and implemented. As a result, this domain evaluates whether their perspectives and their impact were explored and recognized in the writing up of the recommendations. In this domain, the BSH CPG scored 85%.

AGREE-REX domain 3. Implementability

The items "purpose" and "local application and adoption" are part of this implementability domain. This domain evaluates the suitability of guideline recommendations for patients/populations and/or healthcare systems that uptake them, as well as the level of shift from current practice. Furthermore, the guideline should clarify key factors that will contribute to its successful dissemination. Furthermore, the purpose item assesses whether weather guideline recommendations are aligned with the guidelines' implementation goals. In this domain, the BSH CPG scored 92%.

AGREE-REX overall assessment

This domain determined whether raters would recommend the BSH CPG in both the appropriate context and the raters' healthcare context. All five raters agreed that they recommend this CPG for use in clinical practice.

The checkUp results

The compliance of the BSH CPG for SCD in pregnancy with the CheckUp Tool was represented in table 4. Out of the 16 CheckUp Items 13 (81%) were clearly reported in the BSH CPG article, BSH official website, and related documents.

Item	Assessment	Reported on Page Number	Notes
1. The updated version can be distinguished from the previous version of the CPG	☒ Yes ☐ No ☐ Unclear ☐ NA	Literature review details, introduction Page 980	
2. The rationale for updating the CPG is reported.	☒ Yes ☐ No ☐ Unclear ☐ NA	The previous version (RCOG) CPG was due for revision in 2014 and The British Society for Haematology had agreed to take over and update this CPG. Page 980	Further details about this updated CPG were provided in the published commentary: Standardizing care of those at great risk: the importance of sickle cell in pregnancy practice guidelines by Stratton in 2021 https://doi.org/10.1111/bjh.17667
3. Changes in the scope and purpose between the updated and previous version are described and justified	☒ Yes ☐ No ☐ Unclear ☐ NA	Introduction: Updates from the previous guideline Page 980	Further details about this updated CPG were provided in the published commentary: Standardizing care of those at great risk: the importance of sickle cell in pregnancy practice guidelines by Stratton in 2021 https://doi.org/10.1111/bjh.17667 'It was Written from the perspective of haematologists'.

4. The sections reviewed in the updating process are described	☒ Yes ☐ No ☐ Unclear ☐ NA	Introduction: Updates from the previous guideline Page 980	The following updates were mentioned: • Pre-implantation genetic diagnosis (PGD), • More comprehensive information on pre-conceptual screening and medication review. • Updated information on thromboprophylaxis, aspirin and vitamin D, • Changes to advice on antenatal care including frequency of ultrasonography (USS)scanning. • Reference to the most recent NICE and RCOG guideline
5. Recommendations are clearly presented and labelled as new, modified, or not changed. Deleted recommendations are clearly noted.	☐ Yes ☐ No ☒ Unclear ☐ NA		• Recommendations are highlighted in bulleted bold statements under the subtitle (recommendations) but are labelled new, modified, or not changed. • Only the updated topics are mentioned in the introduction section.
6. Changes in the recommendations are reported and justified.	☒ Yes ☐ No ☐ Unclear ☐ NA		• The updated topics are mentioned in the introduction section. The BSH CPG Committee retrieved 218 papers for this update. • Additional details were provided in the published commentary: Standardizing care of those at great risk: the importance of sickle cell in pregnancy practice guidelines by Stratton in 2021 https://doi.org/10.1111/bjh.17667
7. The panel participants in the updated version are described.	☒ Yes ☐ No ☐ Unclear ☐ NA	Authors list and Review of the Manuscript Page 980	Eight authors (6 OBGYNE and maternal health experts and two hematology experts were included om behalf of the BSH Guidelines Committee) were stated for the updated BSH CPG article. The manuscript was reviewed by six societies and bodies (Review of the manuscript)
8. Disclosures of interests of the group responsible for the updated version are recorded.	☒ Yes ☐ No ☐ Unclear ☐ NA	Conflicts of interest Page 993	In the official BSH website also there is a declaration of interests: https://b-s-h.org.uk/guidelines/guidelines/gl-management-of-sickle-cell-disease-in-pregnancy/

9. The role of the funding body for the updated version is identified and described.	☒ Yes ☐ No ☐ Unclear ☐ NA	Conflicts of interest Page 993	Conflicts of interest The BSH paid the expenses incurred during the writing of this guidance.
10. The methods used for searching and identifying new evidence in the updating process are described.	☒ Yes ☐ No ☐ Unclear ☐ NA	Literature review details Page 980	The CPG article refers to the BSH official website for further details in the BSH Guidelines Development Process (PDF) and related templates (Proposing and writing a new BSH Guideline) through the link: Proposing and writing a new BSH Guideline | British Society for Haematology (b-s-h.org.uk)
11. The methods used for evidence selection in the updating process are described.	☐ Yes ☐ No ☒ Unclear ☐ NA	Literature review details Page 980	It was mentioned without detail in the CPG article but it links to the BSH official website for further details in the BSH Guidelines Development Process (PDF) and related templates (Proposing and writing a new BSH Guideline) through the link: Proposing and writing a new BSH Guideline | British Society for Haematology (b-s-h.org.uk)
12. The methods used to assess the quality of the included evidence in the updating process are described.	☒ Yes ☐ No ☐ Unclear ☐ NA	The GRADE nomenclature was used to evaluate levels of evidence and strengths of recommendations Page 980	The GRADE Summary of Findings and EtD tables were not reported but further details were provided on the BSH official website for in the general BSH Guidelines Development Process.
13. The methods used for evidence synthesis in the updating process are described.	☒ Yes ☐ No ☐ Unclear ☐ NA	The GRADE nomenclature was used to evaluate levels of evidence and strengths of recommendations Page 980	The GRADE Summary of Findings and EtD tables were not reported but further details were provided on the BSH official website for in the general BSH Guidelines Development Process.
14. The methods used for externally reviewing the updated version are described.	☒ Yes ☐ No ☐ Unclear ☐ NA	Review of the Manuscript Page 980	It was mentioned without detail in the CPG article but it links to the BSH official website for further details in the BSH Guidelines Development Process (PDF) and related templates (Proposing and writing a new BSH Guideline) through the link: Proposing and writing a new BSH Guideline | British Society for Haematology (b-s-h.org.uk)
15. The methods and plan for implementing the change of the updated version in practice are described.	☐ Yes ☐ No ☒ Unclear ☐ NA	An Audit (Microsoft Word) Template was provided in the BSH website: https://b-s-h.org.uk/guidelines/guidelines/gl-management-of-sickle-cell-disease-in-pregnancy/	The template was not mentioned in the CPG article.

16. The plan and methods for updating the new version in the future are reported.	☒ Yes ☐ No ☐ Unclear ☐ NA	Review Process Page 993	Further details were mentioned in the BSH Guidelines Development Process (PDF) through the link: Proposing and writing a new BSH Guideline | British Society for Haematology (b-s-h.org.uk)

Table 4: *Compliance with the Items of the CheckUp Tool.*

Abbreviations: BSH: British Society for Haematology; CPG: Clinical Practice Guideline; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; EtD: Evidence-to-Decision Framework; NA: Not Applicable; OBGYNE: Obstetrics and Gynecology; PDG: Pre-Implantation Genetic Diagnosis; RCOG: Royal College of Obstetricians and Gynaecologists.

Discussion

This review assessed the methodological quality of the BSH 2022 CPG for SCD in pregnancy using the AGREE II Instrument, the clinical credibility and implementability of the CPG using the AGREE-REX Tool in addition to assessing the updating process using the CheckUp Tool. The results of the AGREE II assessments of both CPGs were similar where the BSH and RCOG CPGs scored in Domain 1: Scope and purpose (83%, 89%), Domain 2: Stakeholder Involvement (79%, 76%), Domain 3: Rigor of development (90%, 73%), Domain 4: Clarity and presentation (86%, 83%), Domain 5: Applicability (58%, 46%), Domain 6: Editorial Independence (73%, 77%), and in the first Overall assessment (88%, 79%) respectively [8]. All of the AGREE II Domains scored more than 60% except domain 5.

Differences between the BSH updated version and RCOG previous version of the CPG

On sickle cell disease management in pregnancy, the RCOG introduced its green top CPG in 2011, and the BSH launched its CPG in 2021 [8,12,13]. Most of the recommendations in these two guidelines are common. Both agree on the following information. Chronic complications should be screened and managed to optimize the outcomes. These include annual screening for hepatic, renal, retinal, cardiac, pulmonary hypertension, pulmonary function and iron load [12,13].

Furthermore, look for chronic lung disease, avascular necrosis, and previous stroke history. Actions recommended include echocardiography, oxygen saturations, sleep studies, pulmonary function tests, and a chronic pain clinic referral. If this screening is not done in the last year, it should be conducted pre-pregnancy or early in pregnancy. Discussion on pregnancy and contraception should be part of the annual assessment. The pre-pregnancy clinic should have easy access, and specialists should assess to screen for complications and degree of end-organ damage. Partner testing should be conducted before embarking on the pregnancy. Prenatal or pre-implantation genetic diagnosis should be offered to high-risk couples since the risk of SCD babies. If an affected fetus is identified, the option of termination should be offered, antenatal care by a multidisciplinary team in a tertiary care center, modified medication, discontinuing ARBs, ACEi, Hydroxycarbamide, and Iron chelators. Medication like Folic acid, aspirin (to reduce the risk of preeclampsia), daily antibiotic prophylaxis, and vaccinations for influenza, pneumonia, and hepatitis. Aspirin between 12 weeks to 36 weeks of gestation. Precipitating risk factors for SCD pain crisis should be identified and guarded by preventive measures. These risk factors include hypoxia, stress, anemia, dehydration, cold, and infection. Serial fetal biometry scans every four weeks beyond 24 weeks of gestation should be offered since babies are at risk of IUGR, fetal distress, labor induction, and cesarean section. ABO-compatible, Rh- and Kell-matched, CMV-negative units should be transfused if transfusion is indicated. Time of delivery is agreed upon beyond 38 weeks for a normally grown baby and vaginal delivery is preferred if not contraindicated. Since these are high-risk pregnancies should be delivered in hospitals to manage feto-maternal complications of SCD. Anesthetic assessment in the third trimester. Inform MDT that once she is in labor, blood should be cross-matched.

During labor, risk factors for pain are prevented by good hydration, oxygenation, keeping warm, and continuous electronic fetal monitoring for the baby. While avoiding pethidine, regional analgesia is recommended if a cesarean section is indicated. The delivery position

should be discussed before delivery in patients with a hip replacement for avascular necrosis. Thromboprophylaxis with LMWH should be considered for the duration of admission if the patient is admitted in the antenatal, intrapartum, or postnatal period. SCD patients should be offered thromboprophylaxis from 28 weeks to 6 weeks postpartum. Contraceptive advice by the primary care team should be individualized according to patient choice and disease status, LARC (long-acting reversible contraceptive) methods are preferred, and progesterone-only preparations are associated with a reduction in sickle pain.

This BSH sickle cell disease (SCD) CPG was developed and updated from a previous RCOG Green-top CPG following the standard methodology for producing BSH CPGs.

BSH followed RCOG with some updated modifications in the following points: BSH emphasized that Iron chelators are not recommended during pregnancy due to a lack of safety data. They should be considered potentially teratogenic in the first trimester and should be stopped when a woman is trying to conceive.

Moreover, the liver and cardiac magnetic resonance imaging before conception to highlight those at high risk of iron-related complications, women having sickle cell disease with iron overload, should be carefully radiologically assessed.

If there is evidence of iron overload, BSH declared that this should be treated before conception. Cardiac iron overload is unusual in SCD, but if it occurs, women should be encouraged to chelate rigorously before conception. Third-trimester desferrioxamine can be considered according to BSH guidelines.

New medications, including voxelotor, crizanlizumab, and glutamine, are not approved during pregnancy and should be stopped before conception or when pregnancy is confirmed if unplanned. Although these drugs are not approved for use in the UK at the time of publication, they may be approved at some point, and women may have been prescribed these drugs overseas.

The critical question in managing pregnant women with SCD is the best approach to a blood transfusion during pregnancy. One approach is to give blood only if the clinical situation requires, for example, acute anemia or other acute complications. The other approach is to give blood prophylactically throughout pregnancy. If this approach is used, then further questions include whether simple or exchange transfusion should be used, at what gestation transfusion therapy should be started, and whether there is a target Hb or HbS% that should be used. This decision has been discussed in a previous BSH CPG and a recent American Society of Hematology (ASH) CPG [20,21].

As per the BSH CPG, there is currently insufficient evidence to recommend prophylactic transfusion over standard care (transfusion as required), and while there is some evidence that prophylactic transfusion will reduce vaso-occlusive pain during pregnancy, it is not clear if the benefits of transfusion will outweigh the risks of transfusion (e.g. alloimmunization). The recent ASH guidelines44 concluded that there was insufficient evidence to recommend a strategy of prophylactic transfusion rather than standard care, which is quite a feasible approach.

BSH CPG declares that if the benefits of prophylactic transfusion do not outweigh the risks, standard care is to give transfusion on demand when clinically indicated.

There is little evidence to indicate what target Hb or HbS% should be used for optimal care and most evidence comes from the care of non-pregnant patients with SCD. The randomized trial of transfusion described above46 used a Hb value of < 60 g/l as an indication for simple transfusion, and this level was used in previous RCOG guidance.1 Many clinicians would aim for a higher Hb value during pregnancy, although this will depend on baseline Hb and symptoms of anemia. Women with severe sickle complications (e.g. acute chest syndrome, stroke, or intractable pain) should be treated with transfusion as recommended in non-pregnant patients with SCD.

The BSH CPG is more feasible to be adapted for implementation in our center as it has more emphasized data than RCOG. However, most recommendations are of low certainty, reflecting the limited knowledge base and lack of clinical trials in managing sickle cell disease

in pregnancy. Many recommendations are based on expert opinion. Those guidelines are likely to be updated if further clinical evidence becomes available. There is still a need for well-designed clinical trials in this area to ascertain optimal treatment options.

Conclusion

The updated BSH CPG for sickle cell disease in pregnancy was identified as a high-quality evidence-based CPG using three CPG appraisal tools (AGREE II, AGREE-REX and CheckUp). Both the former RCOG and the updated BSH CPGs emphasized the importance of providing healthcare for pregnant women with SCD through a multidisciplinary team, especially with an obstetrician and midwife experienced in high-risk antenatal care and a hematologist experienced in SCD and hemoglobinopathies.

Declaration of the Conflicts of Interest

None to be declared. All of the authors are staff at King Saud University and King Saud University Medical City. This project is part of a local guideline adaptation project at the same organization.

Authors Contributions

YA conceptualized the study; GE, YA, and KB wrote the first draft of the manuscript; YA, GE, FA, AH, and MA contributed to the quality appraisal of the guideline and YA, GE, KB, and SA to the interpretation of the results and discussion. All authors critically reviewed the final draft of the manuscript.

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