WHO recommendations on the management of sickle-cell disease during pregnancy, childbirth and the interpregnancy period

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Acronyms and abbreviations

AMR	antimicrobial resistance
CERQual	Confidence in the Evidence from Reviews of Qualitative research
CI	confidence interval
DOI	declaration of interest
ESG	Evidence Synthesis Group
EtD	evidence-to-decision
FIGO	International Federation of Gynecology and Obstetrics
GDG	Guideline Development Group
GFR	glomerular filtration rate
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HICs	high-income countries
HIT	heparin-induced thrombocytopaenia
HRP	UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction
IpTp-SP	intermittent prophylaxis with sulfadoxine-pyrimethamine
IV	intravenous
LICs	low-income countries
LMICs	low- and middle-income countries
LMWH	low molecular weight heparin
LOAEL	lowest observed adverse effect level
MVM	maternal vascular malperfusion
NCD	noncommunicable disease
NSAID	nonsteroidal anti-inflammatory drug

NWS	neonatal withdrawal syndrome
OR	odds ratio
PICO	population (P), intervention (I), comparison (C), outcome (O)
PPH	postpartum haemorrhage
QES	qualitative evidence synthesis
RCT	randomized controlled trial
RR	relative risk
SCD	sickle-cell disease
TOLAC	trial of labour after caesarean
UFH	unfractionated heparin
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
VTE	venous thromboembolism
WHO	World Health Organization

Executive Summary

Introduction

Sickle-cell disease (SCD) is a group of autosomal recessive haemoglobin disorders that results from a gene mutation in the β-subunit of haemoglobin (1). It is a common inherited condition worldwide, affecting 7.74 million people (2). SCD is highly prevalent in sub-Saharan Africa, and causes a significant disease burden in other historically malaria-endemic regions of Africa, the Middle East, the Caribbean and South Asia. SCD also affects people in many other countries (2). Between 2000 and 2021, the number of people living with SCD globally increased by 41.4% (2).

SCD is associated with severe anaemia, vaso-occlusive crises, cerebrovascular disease, opportunistic infections, and premature mortality, see Figure 1 (3). In addition, quality of life is significantly reduced and depression is common in patients with SCD (4). Many infectious diseases, such as pneumococcal disease, are more dangerous to people with SCD than those without SCD (5).

As infant and child mortality from SCD decreases due to advances in disease management, the number of people reaching reproductive age with this disorder increases. Pregnancies in women[1] with SCD are associated with increased rates of adverse outcomes (see Figure 1). Maternal mortality is 4- to 11-fold higher in women with SCD than in those without SCD (3, 6, 7). Maternal mortality is even higher in low-income countries (LICs) (7). Other complications of pregnancy increased in women with SCD include pre-eclampsia, stillbirth, preterm birth and small-for-gestational-age babies (8).

No World Health Organization (WHO) guideline exists on the management of SCD in pregnancy. In a review of existing guidelines[2], five guidelines that discussed SCD in pregnancy were found, all of which were from high-income countries (HICs) and four of which were based on consensus rather than systematic review of the evidence. Given that the disease burden of SCD is global, with a majority of cases in low- and middle-income countries (LMICs), guidelines applicable to these environments are needed.

1 The term "women" is used throughout this document to refer to all those who identify as women regardless of sex assigned at birth but recognises that there are other gender diverse individuals who do not identify as women but who have reproductive capacity. The intention is not to exclude their experiences but reflects the current lack of data identifying, and/or reflecting the specific experiences of, gender diverse individuals.

2 Ramson J, Williams MJ. Prioritizing topic areas for the development of World Health Organization recommendations on care for women with noncommunicable diseases in the perinatal period, unpublished.

Target audience

The primary audiences for this guideline are health-care providers responsible for developing national and local health-care protocols and policies, as well as managers of maternal and child health programmes, and policy-makers in all settings. The guideline will also be useful to those directly providing care to women during pregnancy and when giving birth, such as obstetricians, midwives, nurses and general practitioners. Finally, the information in this guideline will be useful for developing clinical tools for pre- and in-service training of health workers and health-system strengthening efforts to enhance their delivery of clinical care.

Guideline development methods

The development of this guideline was guided by the process described in the *WHO handbook for guideline development* (9). The guideline was developed using the following steps: (i) identification of priority questions and outcomes; (ii) retrieval of evidence; (iii) assessment and synthesis of evidence; (iv) formulation of the recommendations; and (v) planning for the dissemination, implementation, impact evaluation and future updating of the recommendations.

De novo systematic reviews were used to prepare evidence profiles for the prioritized questions. The quality of identified scientific evidence underpinning the recommendations was appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and the GRADE Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual) approaches, for quantitative and qualitative evidence, respectively. The GRADE evidence-to-decision (EtD) framework – an evidence-to-decision tool that includes intervention effects, values, resource use, equity and human rights, acceptability and feasibility criteria – was used to guide the formulation of recommendations by the Guideline Development Group (GDG). The GDG comprised an international group of experts and assembled for consideration of these recommendations on 30–31 May 2023, 12–13 December 2023, 8–9 October 2024 and 26–27 November 2024.

Considerations underpinning the recommendations

At the December 2023 GDG meeting, it was agreed that a set of considerations underlying all recommendations be developed and that some background information be included to inform care across the maternity journey for women with SCD. The following points were formulated and agreed by the GDG at the November 2024 meeting.

- In 2020, 95% of maternal mortality occurred in LMICs (10).[3] The 2015 WHO report on inequality in reproductive, maternal, newborn and child health states that "the poorest, the least educated and those residing in rural areas have lower health intervention coverage and worse health outcomes than the more advantaged" (11). This report also found that preventing and reducing morbidity and mortality in childbirth can play a key role in reducing overall health inequities.
- SCD is highly prevalent in sub-Saharan Africa, and causes a significant disease burden in other historically malaria-endemic regions of Africa, the Middle East, the Caribbean and South Asia. SCD also affects people in many other countries (2). Globally, the number of people living with SCD increased by 41.4% between 2000 and 2021 (2). Pregnancies in women with SCD are associated with multiple morbidities that affect outcomes for women and babies. Maternal mortality is 4- to 11-fold higher in women with SCD than in those without SCD (6, 7), and is even higher in LICs (7). Other complications of pregnancy that are increased in women with SCD include pre-eclampsia, stillbirth, preterm birth and small-for-gestational-age babies (8).
- SCD is a neglected condition, and inequalities in access to adequately resourced care for SCD reflect its geographical distribution (12). This guideline aims to address the most serious problems for pregnant women with SCD and propose interventions that have the greatest potential to improve outcomes for women and babies. The guideline is intended for use in all countries but especially in lower-resource settings. All women have the right to the highest attainable standard of physical and mental health, irrespective of SCD or pregnancy status (13). In some settings, however, the current level of care may not adequately meet the needs of pregnant women with SCD.
- WHO envisions a world where every pregnant woman and newborn baby receives quality care throughout the pregnancy, childbirth and postnatal period (14). *WHO recommendations for a positive pregnancy experience* highlight the importance of providing effective communication about physiological, biomedical, behavioural and sociocultural issues, as well as effective support, including social, cultural, emotional and psychological support, to pregnant women in a respectful way (14).
- In recognition of research indicating that women value a positive childbirth experience, WHO also emphasizes that women's experience of pregnancy care is critical and not just complementary to the provision of routine clinical practices (15). Although women with SCD may face higher risks during pregnancy, it remains important to centre the individual woman's values and preferences and facilitate the most positive childbirth experience that is possible while managing these risks effectively.

3 Since the GDG discussions, maternal mortality estimates have been updated. In 2023, approximately 92% of maternal deaths occurred in LMICs. see, https://iris.who.int/bitstream/handle/10665/381012/9789240108462-eng.pdf?sequence=1

- There is potential to improve outcomes for women and babies by taking a life-course approach that integrates care and prevention of noncommunicable diseases, such as SCD, with sexual, reproductive, maternal, newborn and child health care (16).
- People with SCD may experience health-related stigma due to their condition, with contributing factors including race, disease status, socioeconomic status, delayed growth and puberty, and/or having chronic and acute pain that needs to be managed with opioids (17). Women with SCD who become pregnant may experience additional stigma (18). Stigma impacts social relationships (with friends, family, co-workers, peers and the wider community), psychological well-being, physiological well-being, as well as patient–provider relationships and care-seeking behaviours (17). This guideline aims to challenge prejudice and discrimination, raise the profile of the condition, and rally change for people living with SCD.
- In some instances, health-care providers lack knowledge and understanding of SCD and the underlying genetics (18, 19, 20, 21). While highlighting the lack of knowledge, this guideline emphasizes the need for education, training, and accurate and accessible information about SCD among health-care providers.
- In some communities where SCD is highly prevalent, the concept of genetically inherited disease does not align with native or traditional understandings of disease causation (22, 23). Local policy-makers and care providers should be sensitive to these differences in understanding and actively engage with all stakeholders to develop an accurate understanding of SCD that is accessible to members of affected communities.
- Given the multifaceted nature of SCD, care from a variety of specialists is needed, with each addressing different aspects of the disease. A multidisciplinary team caring for women during pregnancy may include an obstetrician, haematologist (preferably the primary haematologist who managed the woman during the pre-pregnancy period) or health-care provider with expertise in SCD, a neonatologist, midwife, public health nurse, pulmonologist, an intensivist/anaesthesiologist and a clinical psychologist.
- Women with SCD experience an array of psychological and emotional challenges during pregnancy and the postnatal period (including after miscarriage or termination) (18). People with lived experience of SCD may require psychological support and counselling to help them cope with the symptoms of SCD and the psychosocial consequences of living with the condition (4, 18, 23). Ideally, such support would be timely, accessible, aim to enhance the quality of life for people with SCD (23) and be provided by skilled practitioners with appropriate training in both genetics and mental health.
- Information is lacking about the safety of many medications in pregnancy and while breastfeeding (24, 25, 26). This has tended to lead to a precautionary approach, whereby women are advised, or decline, to take medications that they rely on when not pregnant, or receive conflicting advice (24). In addition to safety concerns, decisions about dis/continuation of medications in pregnancy should reflect a commitment to equitable access to effective medications for pregnant and breastfeeding women with SCD, and be responsive to the woman's individual risk–benefit preferences. Greater efforts should be made to include pregnant women with SCD in clinical trials.
- People with SCD are more vulnerable to infections, and this susceptibility is even greater in pregnancy (27). Infection prevention and treatment is a key aspect of effective care (23). Pregnant women with SCD need access to local non-pharmacological infection prevention measures such as clean water, sanitation, hygiene and local immunization programmes.

- The normal physiological changes of pregnancy (such as immune-adaptation and hypercoagulable state) may exacerbate the pathophysiological changes characteristic of SCD, compounding the risks to a woman's health due to SCD (8, 27). For women with SCD, the journey to motherhood can involve a series of emotional, physical and practical challenges above and beyond those experienced by women in less vulnerable circumstances (18). While placing a spotlight on the complex interaction between SCD and pregnancy, this guideline aims to provide actionable guidance that can improve outcomes for women with SCD and their babies.

Recommendations

The GDG issued 21 recommendations — eight on medication management, four on pain management, two on fluid management in women hospitalized with SCD, one on thromboprophylaxis in pregnant women hospitalized with SCD, two on fetal monitoring, one each on timing and mode of birth, and two on interpregnancy management.

As there is a paucity of direct empirical evidence on the effectiveness of interventions as part of maternity care for women with SCD, no comment on the strength of the recommendations was possible. Rather, they are underpinned by assessment by the GDG of the balance of health benefits and harms based on physiological understanding of SCD and of pregnancy; human rights and sociocultural acceptability; health equity, equality, and non-discrimination; societal implications; financial and economic considerations; feasibility and health-system considerations; and women's views and preferences.

To ensure that the recommendations are correctly understood and applied in practice, the GDG provided additional remarks. Users of the recommendations should refer to these remarks, which are presented directly beneath the recommendations in Section 3.1.

The recommendations are given below.

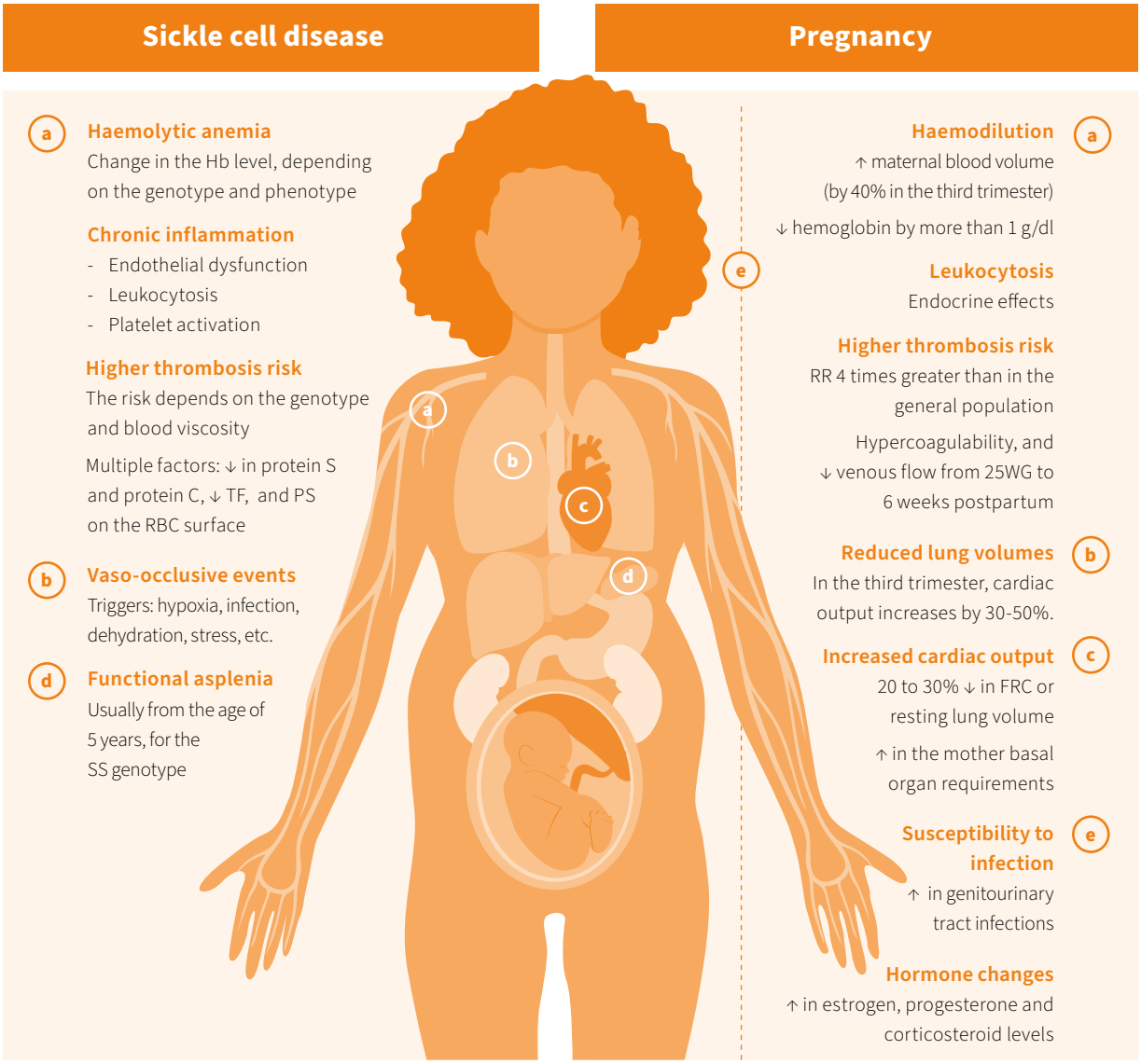
Topic	Recommendation
Medication management for women with SCD presenting for antenatal care	
Folic acid supplementation	1a. Advise pregnant women with SCD living outside malaria endemic areas to continue daily supplementation with up to 5 mg folic acid or to initiate supplementation at this dose as soon as possible. 1b. Advise pregnant women with SCD taking intermittent preventive treatment with sulfadoxine-pyrimethamine that 400 µg folic acid supplementation daily is appropriate, as higher doses may counteract the efficacy of the antimalarial.
Iron supplementation	1c. Advise pregnant women with SCD that iron supplementation is not needed unless there is evidence of iron deficiency. 1d. For pregnant women with SCD who are iron deficient, advise iron supplementation as for the general pregnant population.

Topic	Recommendation
Prophylactic blood transfusion	1e. For pregnant women with SCD and a history of severe intractable crises (i.e. recurrent painful crises and/or events unresponsive to other treatment modalities) or with lived experience of previous benefit from prophylactic transfusion outside of pregnancy, consider prophylactic blood transfusion.
Hydroxycarbamide (hydroxyurea)	1f. For pregnant women with SCD previously controlled with hydroxycarbamide (hydroxyurea), consider continuation or recommencement (after the first trimester) of the medication in the context of shared decision making involving the woman and a multidisciplinary team that includes experts in SCD and pregnancy. Base risk–benefit analyses on the woman's symptom severity, stage of pregnancy and her views and preferences.
Thromboprophylaxis	1g. For pregnant women with SCD (not hospitalized), consider additional risk factors for thromboembolism (e.g. prior venous thromboembolism [VTE] following vaso-occlusive events) and follow local recommendations for initiation of thromboprophylaxis for pregnant women with elevated risk of thrombotic events (e.g. prior VTE, obesity, inherited thrombophilia).
Infection prophylaxis	1h. For pregnant women with SCD, advise against routine infection prophylaxis and implement frequent screening for infection (such as urinary tract infection), using a low diagnostic threshold for bacterial urinary tract infection.
Pain management for pregnant women with SCD	
Pain medication	2a. For pregnant women with SCD who are experiencing acute sickle-related pain, offer timely and optimal pain relief. 2b. When advising use of analgesia, options include oral paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), or opioids at the lowest effective dose for the shortest period of time required to manage pain. 2c. When advising use of analgesia, consider the stage of pregnancy and contraindications for specific medications, the woman's views, preferences and previous experience of the medication, risk of dependence, and availability.
Pain management plans	2d. Collaborate with pregnant women with SCD to develop individualized pain-management plans as early in pregnancy as possible, basing the plan on severity and frequency of pain crises, the woman's views and preferences, and including a multidisciplinary team approach to care.

Topic	Recommendation
Management of women with SCD who are hospitalized during pregnancy	
Fluid management in pregnant women hospitalized with SCD	3a. For pregnant women with SCD hospitalized with vaso-occlusive crisis and requiring intravenous fluid hydration, implement frequent clinical monitoring (such as with lung auscultation, oxygenation/pulse oximetry, respiratory rate) for early identification of fluid overload and pulmonary oedema. 3b. For pregnant women with SCD requiring intravenous fluid hydration in the context of obstetric complications such as pre-eclampsia, implement more intensive monitoring for signs of fluid overload.
Thromboprophylaxis in pregnant women hospitalized with SCD	4. Offer thromboprophylaxis to pregnant women hospitalized with SCD unless contraindications are present.
Fetal monitoring	
Additional fetal monitoring during pregnancy	5a. For pregnant women with SCD without complications (due to SCD or to obstetric causes), offer growth/biometric scans to identify fetal growth restriction every four weeks from 24 until 32 weeks' gestation, and then every three weeks until birth. 5b. For pregnant women with SCD with complications (due to SCD or obstetric causes), offer individualized intensive fetal monitoring to guide management, taking into consideration the woman's views and preferences, and the availability of equipment and staff skilled in their use.
Care around birth	
Timing of birth	6. When making decisions about the timing of birth (awaiting spontaneous labour or planned birth) for women with SCD, take an individualized approach based on the anticipated balance of the benefits of continuing pregnancy to allow fetal maturation and the risk of maternal and neonatal morbidities associated with continuation of the pregnancy, and the woman's views and preferences.
Mode of birth	7. Base decisions about mode of birth for women with SCD on the presence or absence of medical or obstetric indications for caesarean birth, availability of local resources (including those required by women to make informed decisions), as well as the woman's views and preferences. In the absence of medical or obstetric indications for caesarean birth, vaginal birth is preferable.

Topic	Recommendation
Interpregnancy management	
Interpregnancy care	8a. Offer women with SCD in the immediate postnatal period and up to six weeks after childbirth care in addition to that outlined in WHO recommendations on maternal and newborn care for a positive postnatal experience (28): • to manage and treat SCD and its complications, using evidence-based interventions including disease-modifying agents such as hydroxycarbamide (hydroxyurea) and pain-management strategies; • to prevent morbidities such as thrombotic events by considering the need for and initiating thromboprophylaxis, as per local recommendations; • to guide choice of contraceptive methods; • to screen the newborn for SCD; and • to guide counselling on the safety of breastfeeding for her baby.
Health service programs	8b. For women with SCD, integrate care across the life course, including sexual and reproductive health care, with specialized disease care, which may include: supporting optimal health; providing pre-pregnancy counselling and guidance on pregnancy planning; and optimizing treatment across the reproductive continuum.

Figure 1: Pathophysiological interactions between pregnancy and sickle cell disease



Abbreviations: ↓: decrease, ↑: increase, FRC: Functional Residual Capacity, Hb: haemoglobin, IUGR: intrauterine growth restriction, PS: phosphatidylserine, RBC: red blood cell, RR: relative risk, SS: homozygous sickle haemoglobin, TF: tissue factor, WG: weeks gestation

Diagram adapted from Joseph L, et., al (3).

1 Introduction

1.1 Background

Sickle-cell disease (SCD) is a group of autosomal recessive haemoglobin disorders that results from a gene mutation in the β-subunit of haemoglobin (1). It is a common inherited condition worldwide, affecting 7.74 million people (2). SCD is highly prevalent in sub-Saharan Africa, and causes a significant disease burden in other historically malaria-endemic regions of Africa, the Middle East, the Caribbean and South Asia. SCD also affects people in many other countries (2). Between 2000 and 2021, the number of people living with SCD globally increased by 41.4% (2).

SCD is associated with severe anaemia (See Figure 1), vaso-occlusive crises, cerebrovascular disease, opportunistic infections, and premature mortality (3). In addition, quality of life is significantly reduced and depression is common in people with SCD (4). Many infectious diseases, such as pneumococcal disease, are more dangerous to people with SCD than those without SCD (5).

As infant and child mortality from SCD decreases due to advances in disease management, the number of people reaching reproductive age with this disorder increases. Pregnancies in women with SCD are associated with increased rates of adverse outcomes (See Figure 1). Maternal mortality is 4- to 11-fold higher in women with SCD than in those without SCD (6, 7). Maternal mortality is even higher in LICs (7). Other complications of pregnancy include pre-eclampsia, stillbirth, preterm birth and small-for-gestational-age babies (8).

Steps towards improving the management of SCD during pregnancy and childbirth would significantly contribute to reducing maternal mortality and morbidity. Likewise, an improvement in the overall quality of maternal health care to prevent and treat complications of SCD in pregnancy is critical to attaining the Sustainable Development Goals health targets (29) and the targets and indicators of WHO's *Thirteenth General Programme of Work* (30), particularly those for achieving universal health coverage.

As a fundamental human right, women and adolescent girls are entitled to sexual and reproductive health and rights, including accessing evidence-based care during pregnancy and childbirth (31). Similarly, it is the vision of WHO that "every pregnant woman and newborn receives quality care throughout pregnancy, childbirth and the postnatal period" (32). Thus, where there is evidence to support effectiveness of a feasible intervention to reduce maternal and perinatal mortality and morbidity, it is essential that mothers and their babies have the opportunity to receive such care.

To provide high-quality care, health workers, especially those in LMICs with the greatest burden of maternal mortality and morbidities, need to be up to date on the latest scientific evidence and best practices, and have access to and be trained in the use of life-saving appropriate interventions. Importantly, health managers, policy-makers and other stakeholders who make decisions on maternal and perinatal health service delivery require updated guidance to inform policies and programmes. These efforts can collectively help to optimize quality of care for women and their babies during pregnancy, childbirth and the postnatal period.

Ensuring accessibility and acceptability of interventions to improve maternal and newborn health outcomes is consistent with international human rights laws, which include fundamental commitments of states to enable women and adolescent girls to survive pregnancy and childbirth, to assure their sexual and reproductive health rights, and to live a life of dignity. High-quality health care could reduce the profound inequities in maternal and newborn health globally and is essential for improving pregnancy and birth outcomes.

1.2 Rationale and objectives

In July 2021, the WHO Steering Group convened a scoping meeting – comprising an independent panel of 15 external experts and relevant stakeholders from the six WHO regions – to explore the scope for a new guideline thematic area covering screening for and management of noncommunicable diseases (NCDs) in pregnancy, childbirth, and the postnatal periods.

To inform the discussions, the WHO Steering Group developed two evidence syntheses. These described the existing definitions and concepts related to NCDs in pregnancy (33) and mapped the (then) current guidelines and recommendations related to maternal health and NCDs (34). The “universe” of thematic areas/conditions to be considered for inclusion in guideline development was based upon a review of the indirect maternal conditions. In considering the breadth and depth of potential thematic areas, the scoping group were requested to assess the general prevalence of the conditions, the interaction between the condition and pregnancy, and the potential for intervention during maternal health contacts.

The following topic areas were considered the highest priorities:

- cardiovascular conditions
- diabetes
- respiratory conditions
- haemoglobinopathies
- mental health disorders and substance use.

The management of SCD is the first of these topics to be addressed.

1.3 Target audience

WHO maternal and perinatal health guidelines are relevant to those providing care and support during pregnancy, labour, childbirth and postpartum periods, in any health-care setting.

The primary audience for this guideline includes health-care providers who are responsible for developing national and local health policies related to care during pregnancy, childbirth and the postnatal period, and

those directly providing care to women around the time of birth, including midwives, nurses, general medical practitioners, obstetricians, and managers of maternal and child health programmes, in all settings.

The guideline will also be of interest to professional societies involved in the care of pregnant women, nongovernmental organizations concerned with the promotion of woman-centered maternal care, and implementers of maternal and child health programmes.

1.4 Scope of the recommendations

The recommendations focus on the management of SCD during pregnancy, childbirth and the postnatal period. The priority questions that guided evidence synthesis and decision making for these recommendations are presented below using the Population (P), Intervention (I), Comparison (C), Outcome (O) (PICO) format. The priority outcomes used in decision making are listed in Annex 2.

Priority questions	
1.	In pregnant women with SCD, does medication management affect outcomes compared to usual care?
2.	In pregnant women with SCD, do pain-management plans affect outcomes compared to usual care?
3.	In pregnant women hospitalized with SCD, do fluid-management plans affect outcomes compared to usual care?
4.	In hospitalized pregnant women with SCD, does thromboprophylaxis affect outcomes compared to usual care?
5.	In pregnant women with SCD, does additional fetal monitoring affect outcomes compared to usual care?
6.	In pregnant women with SCD, does indicated delivery at early term (37–38 weeks) affect outcomes compared to no indicated delivery at early term?
7.	In pregnant women with SCD, what are the benefits and harms of caesarean section compared to vaginal birth (including vaginal birth after caesarean section)?
8.	In women with SCD in the postnatal period, do interpregnancy management interventions affect outcomes compared to usual care?

The WHO comprehensive framework for action on accelerating anaemia reduction identified improved screening and management of inherited red blood cell disorders as a key outcome to be addressed (35). As part of that action, a set of comprehensive WHO recommendations on the diagnosis, prevention and management of anaemia in pregnant and postnatal women is in development. This will include questions related to the screening and diagnosis of haemoglobinopathies.[4]

1.5 Persons affected by the recommendations

The population affected by the recommendations is women with SCD who receive pregnancy care and give birth in low-, middle- and high-resource settings.

4 Personal communication, Lisa Rogers, Technical Officer, WHO Department of Nutrition and Food Safety.

2 Methods

The guideline was developed using the process described in the *WHO handbook for guideline development* (9). In summary, the process included: (i) identification of the priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of the recommendations; and (v) planning for the dissemination, implementation, impact evaluation and updating of the recommendations. Six main groups participated in this process — their specific roles are described below.

2.1 Contributors to the guideline

2.1.1 WHO Steering Group

The WHO Steering Group, comprising WHO staff members from the Department of Sexual and Reproductive Health and Research and the Department of Maternal, Newborn, Child and Adolescent Health managed the process. The WHO Steering Group drafted the key research questions in PICO format, identified the systematic review teams and guideline methodologists, as well as members of the Guideline Development Group and the External Review Group. In addition, the WHO Steering Group supervised the retrieval and syntheses of evidence, organized the GDG meetings, finalized the guideline document, and managed dissemination, implementation and impact assessment. The members of the WHO Steering Group are listed in Annex 1.

2.1.2 Guideline Development Group

For the development of this guideline, 15 external experts and relevant stakeholders were invited to participate as members of the GDG. These individuals were drawn from a pool of approximately 50 experts and relevant stakeholders that constitute the WHO Maternal and Perinatal Health GDG Those selected were a diverse group with expertise in research, guideline development methods, and clinical policy and programmes relating to improving the quality of care and outcomes for women with SCD, as well as a representative of the affected population.

The GDG members were selected in a way that, as far as possible, represented a geographic and gender balance and also ensured that there were no important conflicts of interest. While members from areas of high SCD prevalence were sought, the Steering Group was unable to engage members from some geographic areas (notably the South-East Asian region). The GDG comprised 60% women and 40% men.

Based on the documents prepared by the Steering Group, the GDG appraised and interpreted the evidence, and formulated the final recommendations at meetings convened on 30–31 May 2023, 12 – 13 December 2023, 8 – 9 October 2024 and 26–27 November 2024. The group also reviewed and approved the final guideline document. The members of this group are listed in Annex 1.

2.1.3 Evidence Synthesis Group

WHO convened an Evidence Synthesis Group (ESG) composed of guideline methodologists and systematic review teams for the conduct or updating of systematic reviews, appraisal of evidence, and development of the EtD frameworks.

Two technical consultants, Jen Ramson and Myfanwy WIlliams served as the guideline methodologists. They oversaw the appraisal of evidence using the GRADE methodology (36).

To inform this guideline, a systematic review of qualitative evidence on SCD and maternity care was conducted (18). This was led by experts from the University of Central Lancashire with extensive experience in qualitative evidence reviews. In addition, the ESG initiated a new systematic review of economic evaluations for screening and management of SCD in pregnancy (37).

The guideline methodologists worked closely with the ESG to review the evidence and prepare the GRADE EtD frameworks. Members of the ESG attended the GDG meeting to provide an overview of the synthesised evidence, and to respond to technical queries from the GDG. The members of the ESG are listed in Annex 1.

2.1.4 External partners and observers

Representatives of the International Federation of Gynecology and Obstetrics (FIGO), the International Pediatric Association (IPA), the NCD Alliance, the United Nations Children's Fund (UNICEF) and the United States Agency for International Development (USAID)[5] participated in the GDG meetings as observers. These organizations collaborate with WHO Departments in guideline dissemination and implementation, and were identified as significant implementers of the guideline. The list of observers who participated in the GDG meeting is included in Annex 1.

2.1.5 External Review Group

An external review group comprised four technical experts with interest and expertise in the provision of evidence-based care to improve the quality care and outcomes for women with SCD. The members had no important conflicts of interest. The Group comprised 75% women and 25% men. The experts reviewed the final document to identify any factual errors and commented on the clarity of language, contextual issues and implications for implementation. They ensured that the decision-making processes had considered and incorporated contextual values and the preferences of persons affected by the recommendations, health-care providers and policy-makers. It was not within the remit of this group to change the recommendations that were formulated by the GDG. Members of the External Review Group are listed in Annex 1.

5 USAID participated as an observer in discussions prior to January 2025.

2.2 Evidence identification and retrieval

Evidence to support the development of the guideline recommendations was derived from several sources by the systematic review teams working in collaboration with the WHO Steering Group.

2.2.1 Evidence on effectiveness

To inform the development of the recommendations, WHO commissioned a set of eight *de novo* systematic reviews on the management of SCD in pregnancy, during childbirth and in the interpregnancy period.

External groups of systematic reviewers were asked to prepare review protocols with a clear PICO question and criteria for identification of studies, including search strategies for different bibliographic databases, methods for assessing risk of bias and a data analysis plan (38, 39, 40, 41, 42, 43, 44, 45). The WHO Steering Group and the guideline methodologists reviewed and endorsed the protocols before the systematic reviews were conducted.

The search strategies employed to identify the studies and the specific criteria for inclusion and exclusion of studies are described in the individual systematic reviews. Studies from low-, middle- and high-income countries were considered and there were no language restrictions. The entire systematic review development process was iterative, with the systematic reviewers and guideline methodologists constantly communicating with the WHO Steering Group to discuss challenges and agree on solutions.

There was a paucity of evidence across the systematic reviews, with only one of the eight reviews finding randomized controlled trial (RCT) and non-randomized evidence, and two reviews finding one non-randomized study of interventions each. The remaining five reviews found no studies eligible for inclusion.

2.2.2 Evidence on values, resource use and cost–effectiveness, equity and human rights, acceptability and feasibility

Values, equity and human rights, acceptability and feasibility

The qualitative evidence synthesis (QES) explored the views and experiences of women with SCD during the antenatal, intrapartum and postnatal phases of maternity care and of the health-care providers caring for these women (18). This review was the primary source of evidence on values, equity and human rights, acceptability, and feasibility.

Resource use and cost–effectiveness

The evidence synthesis team initiated a new systematic review of economic evaluations for screening, management and treatment for women with SCD (37). *The review aimed to:*

- synthesize the available evidence from economic evaluations of interventions to screen/diagnose, treat and/or manage SCD during pregnancy
- assess the methodological quality of the economic evaluation studies
- identify the gaps in the evidence from economic evaluations of interventions to manage SCD during pregnancy.

2.3 Quality assessment and grading of the evidence

2.3.1 Quality assessment of primary studies included in the reviews

For the systematic reviews of effectiveness evidence, where eligible RCTs were identified, two reviewers independently assessed the risk of bias using the revised Cochrane risk-of-bias tool (RoB 2.0). For non-randomized studies, the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool was used. Any disagreement was resolved by discussion or by involving a third assessor.

For each included RCT and each outcome, domains of bias explored were: randomization process; identification or recruitment of individual participants within clusters; deviations from intended interventions; missing outcome data; measurement of the outcome; selection of the reported result; and overall bias.

For non-randomized studies, domains of bias explored were: confounding; selection of participants into the study; classification of interventions; deviations from intended interventions; missing data; measurement of outcomes; selection of the reported result; and overall bias.

The quality of studies included in the QES was appraised using the GRADE-CERQual tool (46) as outlined below.

The cost–effectiveness systematic review used the extended Consensus on Health Economics Criteria list (47) for assessing the quality of studies.

2.3.2 Assessment of certainty of the effectiveness evidence

For the effectiveness evidence, the certainty of evidence for a given outcome was rated using the standard GRADE approach based on consideration of study design limitations (risk of bias), inconsistency (heterogeneity or variability in results), indirectness (differences in study populations), imprecision (small study populations and few events) and publication bias (9).

Where possible, summary of findings tables were prepared using GRADEpro software (48). These included the effect estimates (expressed as relative and absolute risk), explanations of the certainty assessments, and an overall certainty rating for each outcome.

GRADE certainty of the evidence

The certainty of evidence for each outcome was rated as 'high', 'moderate', 'low' or 'very low' as defined by the GRADE methodology:

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate certainty**: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low certainty:** Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect; and
- **Very low certainty:** We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Note that assessment of the certainty of the evidence was only possible for two comparisons where RCT evidence was identified and one where non-randomized evidence was analysed.

2.3.3 Assessment of the certainty of (confidence in) the qualitative evidence

The findings of qualitative studies included in the QES were appraised using the GRADE-CERQual tool (46). The GRADE-CERQual tool, which uses a similar conceptual approach to other GRADE tools, provides a transparent method for assessing and assigning the level of confidence that can be placed in evidence from reviews of qualitative research. The systematic review team used the GRADE-CERQual tool to assign a level of confidence to each review finding according to four components: methodological limitations of the individual studies; adequacy of data; coherence; and relevance to the review question of the individual studies contributing to a review finding.

The confidence of evidence for each review finding is rated as 'high', 'moderate', 'low' or 'very low' (46):

- **High confidence:** It is highly likely that the review finding is a reasonable representation of the phenomenon of interest;
- **Moderate confidence**: It is likely that the review finding is a reasonable representation of the phenomenon of interest;
- **Low confidence**: It is possible that the review finding is a reasonable representation of the phenomenon of interest;
- **Very low confidence**: It is not clear whether the review finding is a reasonable representation of the phenomenon of interest.

2.4 Formulation of the recommendations

The WHO Steering Group supervised the preparation and finalization of summary of findings tables and narrative evidence summaries in collaboration with the guideline methodologists using the GRADE EtD framework (49). The EtD framework includes explicit and systematic consideration of evidence on the intervention in terms of specified domains: effectiveness, values, resources, equity and human rights, acceptability and feasibility. Using the EtD framework template, the Steering Group and guideline methodologists created summary documents for each priority question covering evidence on each domain. For each priority question, judgements were made on the impact of the intervention on each domain, in order to inform and guide the decision-making process.

The WHO Steering Group provided the EtD frameworks for discussion, including evidence summaries and summary of findings tables, to GDG members one week before the GDG meetings. The GDG members were asked to review and electronically provide comments on the documents before the GDG meeting. During the online meetings of the GDG (30–31 May 2023, 12–13 December 2023, 8–9 October 2024 and 26–27 November 2024), under the leadership of the GDG chairperson, the GDG members collectively reviewed and discussed the frameworks.

The purpose of the meetings was to formulate and reach consensus on recommendations, based on explicit consideration of the range of evidence presented in the EtD frameworks and the judgements of the GDG members.

In formulating the recommendations, the GDG used the GRADE EtD frameworks and considered separately the synthesized evidence on effectiveness of the intervention, values of stakeholders, resource use and cost–effectiveness of the intervention, acceptability and feasibility of the intervention, and the impact of the intervention on equity and human rights. For each of these domains, the certainty of evidence was evaluated using methods that were appropriate to the available supporting evidence synthesis (such as GRADE or GRADE CerQual) and the GDG made judgements on the effects of an intervention across these domains.

Across the eight EtD frameworks reviewed by the GDG, there was a lack of direct evidence on the effectiveness of all but three interventions (prophylactic transfusion, iron supplementation, and caesarean section). All available direct evidence was assessed to be very low or low certainty. For all frameworks, the GDG considered that there was probably no important uncertainty or variability in how much women with SCD (and their families) value the main outcomes associated with the interventions, and that the impact of the intervention on equity varies. There was no direct evidence on the cost–effectiveness, acceptability or feasibility of the reviewed interventions across the frameworks.

In the absence of direct evidence for most interventions, the GDG drew on the available evidence on physiological changes in pregnancy, management of SCD in the general SCD population, safety and effectiveness of interventions in the general pregnant population, and relevant existing WHO guidance to formulate their recommendations. The GDG did not comment on the strength of the recommendations as they are all are based on indirect evidence and the deliberations of the GDG.

2.5 Management of declaration of interests

WHO has a robust process to protect the integrity of its normative work, as well as to protect the integrity of the individual experts with whom it collaborates. WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to an actual or ostensible conflict of interest. The disclosure and the appropriate management of relevant financial and non-financial conflicts of interest of GDG members and other external experts and contributors are a critical part of guideline development at WHO. According to WHO regulations, all experts must declare their interests prior to participation in WHO guideline development processes and meetings according to the guidelines for declaration of interest for WHO experts (9). All GDG members were therefore required to complete a standard WHO declaration of interest form before engaging in the guideline development process and before participating in guideline-related processes. A short biography of the GDG members was also published on the WHO's sexual and reproductive health website for two weeks for public review and comments prior to GDG meetings.

The WHO Steering Group reviewed all declarations before finalizing the experts' invitations to participate. Where any conflict of interest was declared, the WHO Steering Group determined whether such conflicts were serious enough to affect an expert's objective judgement in the guideline and recommendation development process. To ensure consistency, the WHO Steering Group applied the criteria for assessing the severity of conflicts of interest as outlined in the *WHO handbook for guideline development* (9) to all participating experts. All findings from the declarations of interest were managed in accordance with WHO procedures to ensure that the work of WHO and the contribution of its experts is, actually and ostensibly, objective and

independent. Where conflicts of interest were not considered significant enough to pose any risk to the guideline development process or to reduce its credibility, experts were only required to openly declare such conflicts of interest at the beginning of the GDG meeting and no further actions were taken. Annex 3 shows a summary of the declaration of interest statements and how conflicts of interest declared by invited experts were managed by the WHO Steering Group.

2.6 Decision making during the GDG meetings

The GDG meetings were designed to allow participants to discuss the supporting evidence and to reach a consensus on the final wording of each recommendation. Consensus was defined as the agreement by three quarters or more of the GDG, provided that those who disagreed did not feel strongly about their position. No GDG member expressed opposition to the recommendations.

2.7 Document preparation and peer review

The WHO Steering Group made a draft version of the EtD framework available to the participants one week before the meeting for their comments. During the meeting, the framework was modified in line with the participants' deliberations and remarks. Following the meeting, the WHO Steering Group worked with the guideline methodologists to prepare a full guideline document to accurately reflect the deliberations and decisions of the participants. The draft document was sent electronically to GDG members for their final review and approval. The final document was also sent for peer review to four external independent experts who were not involved in the development of the guideline. The WHO Steering Group evaluated the advice of the peer reviewers for inclusion in this document. After the meetings and external peer reviews, the modifications made by the WHO Steering Group to the document consisted only of the correction of factual errors and edits to address any lack of clarity.

3 Recommendations and supporting evidence

The GDG issued 21 recommendations – eight on medication management, four on pain management, two on fluid management in women hospitalized with SCD, one on thromboprophylaxis in pregnant women hospitalized with SCD, two on fetal monitoring, one each on timing and mode of birth, and two on interpregnancy management. This section outlines the recommendations corresponding to the priority questions. No comment has been made on the strength of the recommendations as, in the absence of direct empirical evidence, all recommendations are based on indirect evidence and the deliberations of the GDG.

To ensure that the recommendations are correctly understood and appropriately implemented in practice, additional 'remarks' reflecting the summary of the discussions by the GDG are included. The recommendations should be applied in conjunction with the implementation considerations.

The EtD frameworks – presenting the available effectiveness evidence, the balance between the desirable and undesirable effects, values of stakeholders, resource requirements, cost–effectiveness, acceptability, feasibility and equity, and human rights that were considered in formulating each recommendation – are presented separately as a Web Annex to this document.

3.1 Recommendations

3.1.1 Medication management for women with SCD presenting for antenatal care

Various medications have been used in the management of SCD in the non-pregnant population. Optimal management to improve the health and well-being of people affected by SCD includes preventive care measures, symptom control, and management of disease complications. These strategies may need to be altered in pregnancy as physiological changes in pregnancy affect symptomology and the natural history of end-organ complications. The effect of treatments on the fetus is also a primary consideration.

The following advice from the GDG is for care above and beyond routine care in pregnancy.

Vitamins and minerals

Folic Acid

Recommendations — folic acid supplementation

1a. Advise pregnant women with SCD living outside malaria endemic areas to continue daily supplementation with up to 5 mg folic acid or to initiate supplementation at this dose as soon as possible.

1b. Advise pregnant women with SCD taking intermittent preventive treatment with sulfadoxine-pyrimethamine that 400 µg folic acid supplementation daily is appropriate, as higher doses may counteract the efficacy of the antimalarial.

Rationale

- In the absence of direct empirical evidence on folic acid supplementation in pregnant women with SCD, the GDG developed these recommendations based on the available physiological evidence on folic acid supplementation in the general population with SCD and the general pregnant population, and existing WHO guidance on folic acid supplementation in pregnant women with SCD taking intermittent preventive treatment with sulfadoxine-pyrimethamine.

Remarks

Folic acid supplementation in the general population with SCD

- Chronic haemolytic anaemia and increased red blood cell production and turnover in SCD are thought to increase the requirements for folate, a water-soluble family of compounds that is essential for red blood cell production (50, 51). There is, however, limited evidence that folic acid supplementation improves haematological or clinical outcomes in individuals with SCD (50).
- Outside of pregnancy, individuals with SCD commonly take 1 mg of folic acid daily (50). Guidance from the WHO African region is that supplementation of folic acid at 5 mg a day for 10 to 20 days a month be used in the general SCD population to prevent worsening anaemia (23). There are, however, some concerns regarding high folate concentrations in populations with SCD in countries with national programmes of refined-grain folic acid fortification (see section on *Folic acid fortification* below) (52).

Folic acid during pregnancy

- Low folic acid levels during pregnancy are associated with anaemia and fetal neural tube defects (53).
- In the general pregnant population, WHO recommends daily folic acid supplementation of 400 µg or weekly supplements of 2.8 mg (14).

Higher-dose folic acid supplementation

- Folic acid is generally considered safe, with an internationally recognized tolerable upper intake level of 1 mg/day and the lowest observed adverse effect level (LOAEL) of 5 mg/day (54, 55). The LOAEL was set by the United States Institute of Medicine at 5 mg/day based on case studies and small observational studies demonstrating that folate doses >5 mg/day from supplemental or fortified foods had been shown to exacerbate or precipitate neuropathy in vitamin B12-deficient individuals (54). Although there are no long-term follow-up studies of offspring exposed to higher doses of folate, there is no evidence of direct toxicity even with folate doses of 15–100 mg/day (56, 57, 58).

- A 2015 systematic review found high-quality evidence that periconception folic acid supplementation prevents neural tube defects compared to no supplementation (relative risk [RR] 0.31, 95% confidence interval [CI] 0.17 to 0.58) but no additional protection was provided with higher doses of folate in the general pregnant population (59). However, the Medical Research Council Vitamin Study, a large randomized controlled trial conducted in seven mostly high-income countries (n=1195), demonstrated that high-dose folic acid (4 mg/day) resulted in a 72% relative risk reduction (95% CI 88% to 29%) for neural tube defects in women with a previously affected pregnancy (60). The 4 mg dose was selected because this was already available as a tablet and was not based on prior dose-finding studies. The authors suggested that the 4 mg dose of folate was responsible for driving the reduction in neural tube defects (60, 61).
- Although some studies have suggested a link between periconceptual high-dose folic acid supplementation and longer-term outcomes, including asthma in the offspring (62, 63) and maternal malignancy, causality has not been established and the consensus is that high-dose folic acid (e.g. 5 mg daily) is generally safe (64).
- The GDG acknowledged that other guidelines have recommended folic acid supplementation at higher doses (5 mg daily) prior to, and during, early pregnancy for women likely to have low folate levels, such as women with diabetes (65), women taking medications for epilepsy (66), and women with obesity (67).

Availability of folic acid supplements

- Folic acid supplements at doses of up to 5 mg are readily available, as separate supplements or within prenatal vitamin formulations.

Folic acid fortification

- There is substantial heterogeneity in folic acid fortification policies globally (68). Among 193 countries examined up to 31 July 2023, 69 implemented mandatory folic acid fortification, 47 had voluntary fortification, and 77 had no fortification (accounting for 32%, 53% and 15% of the global population, respectively) (68). In areas with a high burden of SCD, fortification was mandatory in most of western, eastern and southern sub-Saharan Africa and the Middle-East; voluntary in India, Saudi Arabia and Sudan; and there was no fortification in northern or central sub-Saharan Africa (68). An Australian study suggests that the introduction of folic acid food fortification increased maternal folate by 63% and reduced the effect of supplementary folic acid (69).

Folic acid supplementation and malaria

- Women with SCD living in malaria-endemic regions remain at risk for malaria infection. The *WHO Guidelines for malaria* recommend antimalarial medicine at predetermined intervals to reduce disease burden in pregnancy, and adverse pregnancy and birth outcomes (70). The only currently available regimen is intermittent prophylaxis with sulfadoxine-pyrimethamine (IpTp-SP).
- The GDG acknowledged that the evidence underlying the recommendation for IpTp-SP did not specify the subpopulation of pregnant women with SCD living in endemic areas (71). However, the GDG also acknowledged the availability of direct moderate-certainty evidence suggesting the reduction of malaria infection at delivery (and the risks of malaria-induced anaemia) and the potential for reduction of low birthweight infants in high-burden areas (*low certainty*). Therefore, in the absence of direct evidence regarding the use of folic acid supplementation for pregnant women with SCD, the GDG considered the

evidence that doses of folic acid of 5 mg or more daily counteract the efficacy of IpTp-SP as an antimalarial (72) and thus reaffirms the existing WHO recommendation that only low-dose formulations of folic acid (i.e. 400 µg daily) be co-administered with sulfadoxine-pyrimethamine (70).

Further research

- The GDG noted the lack of evidence on folic acid supplementation dose among women with SCD living in malaria-endemic areas.

Iron

Recommendation — iron supplementation

1c.	Advise pregnant women with SCD that iron supplementation is not needed unless there is evidence of iron deficiency.
1d.	For pregnant women with SCD who are iron deficient, advise iron supplementation as for the general pregnant population.

Rationale

- In light of very limited direct empirical evidence available on iron supplementation in pregnant women with SCD, the GDG developed this recommendation based on the available physiological evidence on iron homeostasis, iron requirements in the general population with SCD, and iron requirements in pregnancy.

Remarks

Iron homeostasis

- Iron levels in the body are balanced through the absorption of dietary iron, iron recycling, utilization and loss. As humans are unable to excrete iron, iron homeostasis must be maintained by regulating the amount of iron that is absorbed from the diet by the absorptive intestinal cells (enterocytes) and the amount of iron that may be utilized or stored by extraintestinal tissues (73).

Iron requirements in the general population with SCD

- People with SCD often receive blood transfusions, either for treatment or prophylaxis. Repeated blood transfusions are associated with a risk of iron overload, as transfusions are a much more efficient form of iron uptake than dietary absorption. In addition, chronic haemolysis in SCD increases serum iron, which also contributes to iron overload (74). Iron overload can have serious consequences including organ damage, particularly in the liver and heart (75). Therefore, iron supplementation is not a consideration in the management of SCD, unless iron-deficiency anaemia is identified.

Increased iron requirements during pregnancy

- During pregnancy there is increased need for iron due to the needs of the fetus and placenta, and expansion of the maternal red blood cell mass (76). The duodenum increases iron absorption in pregnancy but increased dietary intake is typically also needed (76). Pregnant women frequently suffer from iron-deficiency anaemia as a result (76).

- Iron-deficiency anaemia in pregnancy is associated with increased rates of adverse maternal outcomes (e.g. pre-eclampsia, placenta previa, caesarean delivery, longer hospitalization, increased antenatal admission, and increased requirement for red blood cell transfusion) and adverse neonatal outcomes (e.g. preterm birth, small for gestational age, a low 5-min Apgar score, and neonatal and perinatal death) (77, 78).
- For women in the general pregnant population, WHO recommends daily supplementation with 30 to 60 mg elemental iron or, in contexts when daily iron is not acceptable to the woman due to side-effects or in areas where prevalence of anaemia is low (e.g. <20%), weekly supplements of 120 mg of elemental iron (14, 35).

Iron supplementation during pregnancy for women with SCD

- The systematic review conducted to inform this guideline found that the effect of iron supplementation compared to placebo on the risk of sickle-cell crisis, maternal postnatal haemoglobin and birthweight is uncertain (one trial; 14 women; *very low certainty*) (45). No other priority maternal or newborn outcomes were reported.
- The GDG noted that, due to the potential for iron overload in women with SCD receiving blood transfusions, confirmation of iron deficiency (rather than other causes of anaemia) is needed before anaemia is treated with iron supplementation. Prenatal vitamins often contain iron and may also contribute to iron overload in women who do not have confirmed iron deficiency.
- WHO recommends the use of ferritin concentrations to assess iron stores in healthy individuals. Because ferritin is an acute phase protein that rises due to the inflammatory process, use of a higher threshold (i.e. 70 µg/L) is recommended under conditions of infection and inflammation to diagnose iron deficiency (79). Additionally, under these conditions a ferritin concentration exceeding 500 µg/L may indicate the risk of iron overload and further clinical and laboratory evaluation is recommended. Although WHO recommends a ferritin cutoff of <15 µg/L for diagnosing iron deficiency in *healthy* women *i*n their first trimester of pregnancy (79), there is no guidance on thresholds for defining iron deficiency or overload specifically for pregnant women with infection or inflammation. There are several changes occurring in pregnancy that may affect plasma or serum ferritin concentrations when assessing iron status, including the physiological rise in acute phase proteins in pregnancy and the expansion of plasma volume in the second trimester (80).

Vitamin D

- WHO recommends against vitamin D supplementation in the general pregnant population (81). As there is no evidence that there is an extra demand for vitamin D among people with SCD, the GDG considered that a recommendation on this topic was not necessary.

Prophylactic blood transfusion

Recommendation — prophylactic blood transfusion

1e. For pregnant women with SCD and a history of severe intractable crises (i.e. recurrent painful crises and/or events unresponsive to other treatment modalities) or with lived experience of previous benefit from prophylactic transfusion outside of pregnancy, consider prophylactic blood transfusion.

Rationale

- In light of limited direct empirical evidence on prophylactic blood transfusion in pregnant women with SCD, the GDG developed this recommendation based on the available evidence on the role of red blood cell transfusion in the management of SCD in the general SCD population and in pregnant women with SCD.

Remarks

Role of red blood cell transfusion in management of SCD

- Red blood cell transfusions in people with SCD may be in the form of simple transfusions or exchange transfusions, either manual or automated (82). Simple transfusions consist of a transfusion of red blood cells only. Manual exchange involves manual phlebotomy followed by a transfusion. Automated exchange involves removal and replacement of red blood cells using an apheresis system (83). Red blood cell transfusion in a person with SCD aims to increase tissue oxygenation; to decrease viscosity by diluting the relative amount of sickle haemoglobin-containing red blood cells; and to suppress endogenous erythropoiesis (82).
- Red blood cell transfusions are used for chronic prophylaxis against vaso-occlusive events in select patients. Chronic transfusion therapy has also been shown to be beneficial in the prevention of stroke (84), recurrent acute chest syndrome (85), sickle-cell crises not responsive to hydroxycarbamide (86), and pulmonary hypertension (87).

Role of red blood cell transfusion in management of SCD during pregnancy

- During pregnancy, when, historically, hydroxycarbamide has been contraindicated, prophylactic blood transfusion has been used to correct anaemia and to reduce the frequency of SCD complications triggered by haemoglobin level, or by the relative proportion of adult or sickle haemoglobin. Guidance from the WHO African region is that a preventive transfusion programme be instituted in addition to specific obstetrical measures (23).

Available evidence on prophylactic red blood cell transfusion in pregnant women with SCD

- The systematic review conducted to inform this guideline found that, compared to usual care (indicated therapeutic transfusion), prophylactic transfusion may reduce the risk of sickle-cell crisis (RR 0.28, 95% CI 0.12 to 0.67; one trial, 72 women; *low certainty*) (45, 88, 89). The effect of prophylactic transfusion on the risk of splenic sequestration, acute chest syndrome and caesarean section is uncertain (one trial; 72 women; *very low certainty*). No other priority maternal outcomes were reported.
- The same systematic review found that the effect of prophylactic transfusion compared to usual care (indicated therapeutic transfusion) on the risk of perinatal death, stillbirth/fetal death, neonatal death, preterm birth (<37 weeks), intrauterine growth restriction, and Apgar score <7 at 5 minutes is uncertain (one trial, 76 fetuses; *very low certainty*) (45). No other priority newborn outcomes were reported.
- An earlier systematic review of nonrandomized studies found that prophylactic transfusions may positively affect several adverse maternal and neonatal outcomes, including maternal mortality, vaso-occlusive pain episodes, pulmonary complications, pulmonary embolism, pyelonephritis, perinatal mortality and preterm birth, in women with SCD (90). It noted, however, that the evidence stems from a relatively small number of studies with methodological limitations and that a prospective, multicentre, randomized trial is needed to determine whether the potential benefits balance the risks of prophylactic transfusions.

- A randomized controlled feasibility trial (n=34) of serial prophylactic exchange transfusion versus standard care in pregnant women with SCD in seven hospitals in the United Kingdom of Great Britain and Northern Ireland (91) was published after the commissioned systematic review search date. Although several priority outcomes were reported, no conclusive indications of effect were found. The authors also call for a multicentre international trial.

Approach to transfusion in pregnant women with SCD

- Decision making about red blood cell transfusion needs to be made on an individual basis, with consideration given to the balance of benefits of transfusion against the risks of transfusion reactions, hyperhaemolysis, blood-borne infections, iron overload and alloimmunization, costs and availability.
- Not all women are able to receive blood transfusions due to multiple red cell alloantibodies or previous severe delayed haemolytic transfusion reactions.
- While iron-chelation therapy is generally used to prevent iron overload in people on chronic simple transfusion, currently used chelators are not recommended in pregnancy.

Availability and safety of red blood cell transfusion

- In many parts of the world, chronic transfusion therapy is either not available, not feasible, or is available but without the possibility of iron-chelation therapy to prevent the inevitable and potentially fatal consequences of iron overload (82). In these settings, the advice in non-pregnant adults has been to consider replacing transfusion therapy with, or transitioning from initial transfusion therapy to, hydroxycarbamide at maximal tolerable doses (82).
- A consistent supply of blood relies on regular donations and effective health-care infrastructure (92). Donation rates differ around the world and some HICs see up to seven times more donations than LICs, where the lack of timely, safe transfusions leads to otherwise avoidable deaths (92). In 2010, WHO passed a resolution on blood products that urges Member States to take all the necessary steps to establish, implement and support nationally coordinated, efficiently managed and sustainable blood and plasma programmes according to the availability of resources, with the aim of achieving self-sufficiency, unless special circumstances preclude it (93).
- Blood products used during pregnancy need to be screened for cytomegalovirus in addition to routine blood-borne pathogens, as recommended in the WHO safe blood transfusion guidelines (94).

Further research

- Questions remain on the effectiveness of prophylactic transfusion for pregnant women with SCD, as well as the best timing, frequency and thresholds, and also regarding comparisons between simple, manual exchange and automatic exchange transfusions.

Disease-modifying agents

Recommendation — hydroxycarbamide (hydroxyurea)

1f. For pregnant women with SCD previously controlled with hydroxycarbamide (hydroxyurea), consider continuation or recommencement (after the first trimester) of the medication in the context of shared decision making involving the woman and a multidisciplinary team that includes experts in SCD and pregnancy. Base risk–benefit analyses on the woman's symptom severity, stage of pregnancy and her views and preferences.

Rationale

- In the absence of direct empirical evidence on the effectiveness and safety of hydroxycarbamide in pregnant women with SCD, the GDG based this recommendation on available evidence from non-randomized studies, and the available evidence on the effectiveness of hydroxycarbamide in the general population with SCD, its safety during pregnancy, and the best interests of the woman and baby.

Remarks

Hydroxycarbamide in the general population with SCD

- Hydroxycarbamide is the most-studied disease-modifying medication for SCD. It has been shown to increase the synthesis of fetal haemoglobin, which inhibits sickling by interfering with the formation of rigid, rod-like polymers of deoxygenated haemoglobin S molecules (95). There is evidence that it reduces the frequency of pain and vaso-occlusive crises (96).

Safety of hydroxycarbamide during pregnancy

- While it is a first-line treatment in the general SCD population, hydroxycarbamide has historically been contraindicated in pregnancy due to teratogenic effects in animal (rat and rhesus monkey) studies (97, 98). It has been noted, however, that the doses used in the studies were 10- to 100-fold higher than therapeutic doses (99).
- Recent non-randomized studies identified through the systematic review commissioned to inform this guideline suggest that the odds of teratogenicity may not be increased (100, 101). The authors of one study, however, reported links with miscarriage, stillbirth and low birthweight after controlling for potential confounders (100). The GDG noted that the study was at high risk of bias, with many pregnancy outcomes being self-reported without medical-record confirmation. A retrospective study on the safety of hydroxycarbamide in the second trimester of pregnancy is currently ongoing (102).
- Guidance from the WHO African region is that hydroxycarbamide treatment be suspended during pregnancy, however timing of treatment suspension is not specified (23). As noted above, the studies suggesting teratogenicity were animal studies (97, 98), used higher doses than those considered therapeutic in humans (99), and teratogenic effects in rats and rhesus monkeys are not proof of teratogenicity in humans (103).

Approaches to use of hydroxycarbamide in pregnancy

- Fetal organs are formed by the end of the first trimester, thus theoretical teratogenic potential is highest during this period. However, the potential risk of miscarriage and stillbirth as well as low birth weight remain throughout pregnancy.

- Given that hydroxycarbamide is the best studied and often only feasible disease-modifying agent for SCD, the GDG considered it unethical to make a blanket recommendation for withholding the medication for the duration of pregnancy. In the context of limited data, the benefits of hydroxycarbamide for symptom control need to be weighed against the potential fetal risks.
- In the context of shared decision making, pregnant women with SCD who have controlled their condition with hydroxycarbamide outside of pregnancy or who are not candidates for transfusion may benefit from counselling on the current state of knowledge regarding its use in pregnancy, including what is both known and unknown, to assist them in making an informed decision about its use.

Further research

- While the above-mentioned retrospective study on outcomes of pregnancies exposed to hydroxycarbamide is expected to be published soon, further research is needed on the effect of hydroxycarbamide and other disease-modifying agents in pregnancy on maternal and fetal/neonatal outcomes.
- Qualitative studies relating to women's informed consent and experiences of hydroxycarbamide are also needed.

Thromboprophylaxis in pregnant women with SCD (not hospitalized)

Recommendation — thromboprophylaxis

1g. For pregnant women with SCD (not hospitalized), consider additional risk factors for thromboembolism (e.g. prior VTE following vaso-occlusive events) and follow local recommendations for initiation of thromboprophylaxis for pregnant women with elevated risk of thrombotic events (e.g. prior VTE, obesity, inherited thrombophilia).

Rationale

- In the absence of direct empirical evidence on thromboprophylaxis in pregnant women with SCD, the GDG based its recommendation on the available physiological evidence on the risk of thromboembolism in the general population with SCD and in pregnant women.

Remarks

Risk of thromboembolism in the general population with SCD

- SCD is a hypercoagulable state involving alterations in platelet function, activation of the coagulation cascade, impaired fibrinolysis, and venous stasis from vaso-occlusion. Consequently, thrombotic events are a common complication in the general population with SCD. Compared to people without SCD, people with SCD have ~3.5-fold increased risk of all-cause thromboembolism (104) and a 50- to 100-fold increased risk of pulmonary embolism (105).

Risk of thromboembolism during pregnancy

- Pregnancy is also a hypercoagulable state. Overall, pregnancy carries a four- to five-fold higher rate of thromboembolism. Thromboembolism is still a rare event, however, occurring in approximately 1/1000 pregnancies (106, 107). Pregnant women are at risk of thromboembolism throughout pregnancy, including the first and second trimesters, with a substantial increase in risk in the third trimester and in the postnatal period (108). Thromboembolism is responsible for 3.2% of maternal mortality globally (109).

- Pregnant women with SCD are at increased risk of pulmonary thromboembolism (RR 7.74; 95% CI 4.65 to 12.89) (110), and all-cause VTE (RR 32.2; 95% CI 9.70 to 107.00) (111). The risk is even higher for women with complicated SCD. The prevalence of VTE was 3.5-fold greater in women with complications such as vaso-occlusive crisis, acute chest syndrome and pneumonia compared to women without these complications (112).
- Significant risk factors for VTE include previous VTE or thrombophilia (113, 114). Other risk factors include obesity (107, 115, 116, 117, 118), age over 35 years 114,117, 119), immobility and long-distance travel (120), admission to hospital (121), and comorbidities — including inflammatory bowel disease (122, 123), urinary tract infection (122), systemic lupus erythematosus, heart disease (114), and pregnancy-induced hypertension/pre-eclampsia (113, 124). SCD (alone) has been identified as conferring an intermediate risk of VTE (odds ratio [OR] 6.70; 95% CI 4.40 to 10.10) (107).
- Women with multiple risk factors may be at greatly increased risk of VTE in pregnancy, especially in the third trimester and postnatally (125).

Considerations in thromboprophylaxis use during pregnancy

- Thromboprophylaxis with direct oral anticoagulants, low molecular weight heparin (LMWH), unfractionated heparin, and warfarin can reduce the risk of thromboembolism, however the antithrombotic benefits need to be weighed against the risk of postpartum haemorrhage (PPH) which may be exacerbated by anticoagulation.
- The use of direct oral anticoagulants such as warfarin) is generally avoided in pregnancy due to their association with adverse pregnancy outcomes, including fetal loss and fetal anomalies (126, 127)[6].
- Unfractionated heparin (UFH), LMWH and danaparoid (a heparinoid) do not cross the placenta and are safe for the fetus (128, 129, 130, 131, 132, 133, 134, 135, 136). LMWH is considered to have a better safety profile than UFH (137, 138).
- LMWHs are eliminated primarily by renal excretion and may accumulate in people with significant renal dysfunction. In the non-pregnant population, it has been suggested that therapeutic dose LMWH not be used in patients with significant renal impairment (e.g. a glomerular filtration rate [GFR] of less than 30 mL/min), although it is recognized that accumulation in people with renal impairment may differ between the various LMWHs (139, 140).
- LMWH is the most frequently used drug for treatment and prevention of VTE in pregnancy, except in people with heparin-induced thrombocytopaenia (HIT), a history of HIT, or significant renal dysfunction. UFH is generally used in people with significant renal dysfunction (140).
- As LMWHs are expensive, especially in LMICs, UFH might be an alternative.
- Thromboprophylaxis late in pregnancy may preclude the use of epidural or spinal anaesthesia at the time of delivery, so discontinuation of any preventative treatment is a consideration, in line with local practice on the use of anticoagulants in pregnancy (141).

6 Exceptions can occur, i.e. women with mechanical replacement cardiac valves require lifelong anticoagulation and pregnancy-specific anticoagulation regimens are needed, which may include the use of warfarin in the second and third trimesters (127).

Infection prophylaxis

Recommendation — infection prophylaxis

1h. For pregnant women with SCD, advise against routine infection prophylaxis and implement frequent screening for infection (such as urinary tract infection),using a low diagnostic threshold for bacterial urinary tract infection.

Rationale

- In the absence of direct empirical evidence on infection prophylaxis in pregnant women with SCD, the GDG based its recommendation on the available evidence on the risks of infection in people with SCD and in pregnant women.

Remarks

Risks of infection in people with SCD

- People with SCD in general have functional asplenia and are at risk of infection, in particular from encapsulated bacteria such as *Neisseria meningitides, Streptococcus pneumonia* and *Haemophilus influenzae*. Compared to people without SCD, individuals with SCD have 36-fold increased odds of invasive *Streptococcus pneumonia* infection and 13-fold greater odds of invasive *Haemophilus influenza* infection (142). People with SCD also have an increased risk of urinary tract infections (143). In adults with SCD, 14–18% of deaths are attributed to infectious causes (144).

Risks of infection in pregnant women

- People with SCD who become pregnant are more vulnerable to infections (27).
- Urinary tract infection is one of the most common infections in pregnancy, with a reported prevalence of 20% among pregnant women and higher prevalence in LICs than in HICs (145).
- Pregnant women with SCD are at increased risk of bacterial infections (OR 2.48) (77).

Infection prophylaxis in people with SCD

- Infection prevention and treatment is a key aspect of effective care for people with SCD. This highlights the need for access to local non-pharmacological infection prevention measures such as clean water, sanitation, hygiene and local immunization programmes. Guidance from the WHO African Region is that specific infection prevention measures for people with SCD include: extended immunization against encapsulated organisms and hepatitis B; antibiotic prophylaxis with penicillin; malaria prevention using physical methods or chemoprophylaxis according to local guidelines; and systematic deworming for children (23).

Antimicrobial resistance

- Prolonged antibiotic use can promote the development of resistance. In a United Kingdom of Great Britain and Northern Ireland cohort of children with SCD, 71% of whom were receiving penicillin prophylaxis, nasopharyngeal carriage of penicillin-resistant *Streptococcus pneumoniae* was observed in 55% of isolates (146). Similarly, in a Ghanaian cohort of individuals with SCD, over a third of *Streptococcus pneumoniae* isolates were resistant to penicillin (147).

- Antimicrobial resistance is a major global public health threat (148). It is important to optimize care for people with SCD, while reducing the development of antimicrobial resistance. *The WHO AWaRe (access, watch, reserve) antibiotic book* (149) provides guidance on the use of "Access" antibiotics, which have a narrow spectrum of activity, lower cost, a good safety profile and generally low resistance potential.

Considerations in women with SCD

- WHO recommends a seven-day antibiotic regimen for all pregnant women with asymptomatic bacteriuria to prevent persistent bacteriuria, preterm birth and low birthweight (14). Antibiotic prophylaxis is only recommended to prevent recurrent urinary tract infections in pregnant women in the context of rigorous research (14).
- Regardless of whether a pregnant woman with SCD is on prophylactic antibiotics, it is important for the health-care provider to have a high degree of suspicion for infection, and to screen and conduct clinical examinations to promptly diagnose and treat any infections, being cognizant of the potential for antibiotic resistance.

3.1.2 Pain management for pregnant women with SCD

Pain medication

Recommendation — pain medication

2a.	For pregnant women with SCD who are experiencing acute sickle-related pain, offer timely and optimal pain relief.
2b.	When advising use of analgesia, options include oral paracetamol, NSAIDs, or opioids at the lowest effective dose for the shortest period of time required to manage pain.
2c.	When advising use of analgesia, consider the stage of pregnancy and contraindications for specific medications, the woman's views, preferences and previous experience of the medication, risk of dependence, and availability.

Rationale

- In the absence of direct empirical evidence to inform a recommendation on pain medications in pregnant women with SCD, the GDG based its recommendation on evidence of the safety of specific pain medications in the general pregnant population, and in the general population with SCD.

Remarks

Sickle-related pain

- Vaso-occlusion can result in crises characterized by acute pain, which is the most common cause of hospitalization for SCD (150). People typically present with severe joint, back, chest or extremity pain. Vaso-occlusive crises may be triggered by infection, temperature extremes, dehydration, hypoxia, acidosis, or may be spontaneous. During pregnancy, sickle-cell crises are the most common maternal complication, occurring in 55.8% of SCD pregnancies (151, 152).
- The *WHO [African Region] SICKLE Package of Interventions for Sickle Cell Disease Management* highlights the importance of managing sickle-related pain within 30 minutes of presentation to care (23). Vaso-occlusive episodes are often an inciting event for acute chest syndrome, which is a leading cause of mortality in SCD (23).

Pain medications in the general pregnant population

- *Paracetamol:* Paracetamol is considered safe for use throughout pregnancy (153).
- *NSAIDs:* The use of NSAIDs during the first trimester is associated with an increased risk of congenital anomalies (154). After 30 weeks of gestation, NSAIDs can lead to premature closure of the ductus arteriosus and neonatal pulmonary hypertension, and reduce fetal renal blood flow and urine production, leading to a reduced amniotic fluid volume (153).
- *Opioids:* For the woman, long-term opioid use during pregnancy can lead to maternal dependence (153). For the neonate, opioid use in pregnancy is associated with low birth weight, preterm birth, stillbirth and maternal death. Neonatal withdrawal syndrome has also been described in neonates with prolonged exposure in utero. The limited data on the safety of opioid analgesics during the first 30 weeks of pregnancy do not indicate an increased risk of fetal toxicity (153). Opioid use, especially around the time of delivery, may lead to neonatal respiratory depression and/or neonatal withdrawal symptoms (153). It is therefore prudent to report maternal opioid use in pregnancy to the neonatal care team.

Pain medications in people with SCD

- The pain of mild sickle-cell crises is generally managed with paracetamol, a NSAID, codeine phosphate, or dihydrocodeine tartrate (155). Severe crises may require the use of morphine or diamorphine hydrochloride; concomitant use of a NSAID may potentiate analgesia and allow lower doses of the opioid to be used (155). Pethidine hydrochloride is generally avoided if possible because accumulation of a neurotoxic metabolite can precipitate seizures; the relatively short half-life of pethidine hydrochloride necessitates frequent injections (155).

Considerations in people with SCD

- Guidance from the WHO African Region is that pain management includes both symptom management and prevention, including use of disease-modifying agents; individualized and tailored treatment; management of pain across different levels of the health system; and response to acute pain crisis that includes rapid assessment of recent analgesic use, rapid administration of therapy, and reassessment and readministration if pain persists (23).
- *NSAIDs:* NSAIDs may be important adjuvant analgesic agents in the management of SCD pain in pregnancy. Concomitant use of a NSAID may potentiate analgesia and allow lower doses of an opioid to be used (155). NSAIDs may be used at the lowest effective dose for the time period needed when other medications are insufficient to control pain (153). The GDG noted, however, that women with SCD may have comorbid kidney disease/renal dysfunction. Use of NSAIDs in individuals with chronic renal disorders is considered contraindicated due to the risks of nephrotoxicity (156).
- *Opioids:* The GDG noted that the WHO [African Region] sickle package of interventions for sickle cell disease management suggests that opioids be made available in centres with physicians.

Pain-management plans

Recommendation — pain-management plans

2d. Collaborate with pregnant women with SCD to develop individualized pain-management plans as early in pregnancy as possible, basing the plan on severity and frequency of pain crises, and the woman's views and preferences, and including a multidisciplinary team approach to care.

Rationale

- In the absence of direct empirical evidence on pain-management plans for pregnant women with SCD, the GDG based its recommendation on indirect evidence on pain-management plans in the non-pregnant SCD population.

Remarks

Pain-management plans in the non-pregnant SCD population

- Outside of pregnancy, individualized pain-management plans have been shown to reduce length of hospital stay, frequency of admissions/readmissions and time to first opioid dose in the emergency department (157, 158, 159).

Aims of pain management plans

- A pain-management plan is a comprehensive and individualized approach with a goal to avoid painful crises, mitigate pain, enhance quality of life, or address other aspects associated with the pain experience. Pain-management plans may address different aspects of the treatment of sickle-cell pain, including supportive, symptomatic, preventative and abortive management (160).

Individualization of components of a pain-management plan

- A pain-management plan can support self-care strategies (based on awareness of precipitating factors such as dehydration, change in altitude, extremes in temperature, infections and physical and psychological stress), as well as providing guidance to health-care providers to support timely interventions responsive to the needs of the individual woman taking into consideration the woman's knowledge of effective pain medications and doses, and past experience with side-effects.
- To be effective, a plan needs to be actionable for the individual woman given her living situation and available resources, while meeting her clinical needs.

3.1.3 Management of women with SCD who are hospitalized during pregnancy

Fluid management in pregnant women hospitalized with SCD

Recommendations — fluid management

3a.	For pregnant women with SCD hospitalized with vaso-occlusive crisis and requiring intravenous fluid hydration, implement frequent clinical monitoring (such as with lung auscultation, oxygenation/pulse oximetry, respiratory rate) for early identification of fluid overload and pulmonary oedema.
3b.	For pregnant women with SCD requiring intravenous fluid hydration in the context of obstetric complications such as pre-eclampsia, implement more intensive monitoring for signs of fluid overload.

Rationale

- In the absence of direct empirical evidence on fluid management in women with SCD hospitalized with vaso-occlusive crisis, the GDG based its recommendations on available evidence in non-pregnant SCD populations and complicated pregnancies in the general pregnant population.

Remarks

Fluid management in non-pregnant people with SCD

- Although helpful to overcome dehydration, intravenous (IV) hydration often leads to adverse outcomes such as fluid overload, pulmonary oedema, increased length of stay, transfer to intensive care unit, and new oxygen requirement (161). Small-scale retrospective studies have failed to conclusively demonstrate its benefits as well as choice of IV fluids, and rate of IV fluid replacement (161).
- A retrospective chart review of volume overload in SCD found no difference in incidence of volume overload for patients treated with 0.9% saline versus 0.65% saline (162). The association with volume of IV fluids given could not be assessed.
- Another chart review study comparing use of normal saline bolus with no bolus suggested that the use of normal saline bolus is associated with poorer pain control in children with SCD and vaso-occlusive pain (163).
- *In vitro* studies suggest that normal saline may worsen sickling compared to hypotonic solutions (164, 165).

Fluid management in pregnancy

- Uteroplacental circulation is reliant on maternal cardiac output, blood pressure and metabolic homeostasis to function correctly and avoid fetal compromise. In addition, the pregnant woman undergoes a number of physiological adaptations that affect fluid management, including an increase in the circulating volume and a reduction in systemic vascular resistance (166).
- There is considerable evidence that volume overload and persistently positive fluid balance are associated with poorer outcomes in non-obstetric intensive care unit admissions (166).
- Due to the factors outlined above, there is a need to carefully calibrate and readjust the rate of IV fluid hydration, guided by clinical assessment. Both rate and volume of fluid administration need to be balanced with the risks associated with administration of IV fluids.

Choice of fluids

- There is limited evidence to guide the choice of fluids in the general pregnant population. In the critically ill pregnant patient, isotonic crystalloids represent a safe initial choice in a wide variety of maternal conditions (166). Other synthetic colloids and starches may be associated with significant risks (166).
- The choice of fluid will be influenced primarily by the prescribing clinician's experience with that particular fluid, its cost and local availability. Fluid choices may include isotonic fluids such as normal saline solution, 5% dextrose in water, lactated Ringer's solution 5% dextrose in water. There is no evidence on the use of hypotonic fluids such as 0.45% saline, 0.25% saline for the management of vaso-occlusive crises in pregnant women with SCD.

Areas for further research

- There is a lack of RCTs and a need for large multicentre trials to assess the best route, quantity and type of fluid replacement for people with SCD with acute painful crises (167).

3.1.4 Thromboprophylaxis in pregnant women hospitalized with SCD

Recommendation — thromboprophylaxis in pregnant women hospitalized with SCD

4. Offer thromboprophylaxis to pregnant women hospitalized with SCD unless contraindications are present.

Rationale

- In the absence of direct empirical evidence on thromboprophylaxis in pregnant women hospitalized with SCD, the GDG based its recommendation on the available physiological evidence on risk of thromboembolism in the general population with SCD and during pregnancy.

Remarks

Risk of thromboembolism in the general population with SCD

- SCD is a hypercoagulable state involving alterations in platelet function, activation of the coagulation cascade, impaired fibrinolysis, and venous stasis from vaso-occlusion. Consequently, thrombotic events are a common complication. Compared to people without SCD, people with SCD have ~3.5-fold increased risk of all-cause thromboembolism (104) and a 50- to 100-fold increased risk of pulmonary embolism (105).

Risk of thromboembolism during pregnancy

- Pregnancy is also a hypercoagulable state. Overall, pregnancy carries a four- to five-fold higher rate of thromboembolism. Thromboembolism is still a rare event, however, occurring in approximately 1/1000 pregnancies (106, 107). Pregnant women are at risk of thromboembolism throughout pregnancy, including the first and second trimesters, with a substantial increase in risk in the third trimester and the highest risk in the postnatal period (108). Thromboembolism is responsible for 3.2% of maternal mortality globally (109).
- Pregnant women with SCD are at increased risk of pulmonary thromboembolism (RR 7.74; 95% CI 4.65 to 12.89) (110), and all-cause VTE (RR 32.2; 95% CI 9.70 to 107.00) (111). The risk is even higher for women with complicated SCD. The prevalence of VTE was 3.5-fold greater in women with complications such as vaso-occlusive crisis, acute chest syndrome and pneumonia compared to women without these complications (112).

- Significant risk factors for VTE include previous VTE or thrombophilia (113, 114). Other risk factors include obesity 107, 115–118), age over 35 years 114,117,119), immobility and long-distance travel (120), admission to hospital (121), and comorbidities — including inflammatory bowel disease (122, 123), urinary tract infection (122), systemic lupus erythematosus, heart disease (114), and pregnancy-induced hypertension/ pre-eclampsia (113,124). SCD (alone) has been identified as conferring intermediate risk of VTE (OR 6.70; 95% CI 4.40 to 10.10) (107).
- Women with multiple risk factors may be at greatly increased risk of VTE in pregnancy, especially in the third trimester and postnatally (125).
- Immobilization during hospitalization is also a risk factor for thromboembolism (168).

Considerations in thromboprophylaxis use during pregnancy

- Thromboprophylaxis with direct oral anticoagulants, LMWH, UFH, and warfarin can reduce the risk of thromboembolism, however the antithrombotic benefits need to be weighed against the risk of PPH which may be exacerbated by anticoagulation.
- Direct oral anticoagulants are generally avoided in pregnancy due to their association with adverse pregnancy outcomes including fetal loss and fetal anomalies (126)[7].
- UFH, LMWH and danaparoid (a heparinoid) do not cross the placenta and are safe for the fetus (128–136). LMWH is considered to have a better safety profile than UFH (137, 138).
- LMWHs are eliminated primarily by renal excretion and may accumulate in people with significant renal dysfunction. In the non-pregnant population, it has been suggested that therapeutic dose LMWH not be used in patients with significant renal impairment (e.g. a GFR of less than 30 mL/min), although it is recognized that accumulation in people with renal impairment may differ between the various LMWHs (139, 140).
- LMWH is the most frequently used drug for treatment and prevention of VTE in pregnancy, except in people with heparin-induced thrombocytopenia (HIT), a history of HIT, or significant renal dysfunction. UFH is generally used in people with significant renal dysfunction (140).
- As LMWHs are expensive, especially in low- and middle-income countries, UFH might be an alternative.
- Thromboprophylaxis late in pregnancy may preclude the use of epidural or spinal anaesthesia at the time of delivery, so discontinuation of any preventative treatment is a consideration in line with local practice on the use of anticoagulants in pregnancy (141).

Areas for further research

- Research is required to determine the most effective thromboprophylaxis schedule for women who are hospitalized with SCD.

7 Exceptions can occur, i.e. women with mechanical replacement cardiac valves require lifelong anticoagulation and pregnancy-specific anticoagulation regimens are needed, which may include the use of warfarin in the second and third trimesters (127).

3.1.5 Additional fetal monitoring during pregnancy

Recommendations — additional fetal monitoring during pregnancy

5a.	For pregnant women with SCD without complications (due to SCD or to obstetric causes), offer growth/biometric scans to identify fetal growth restriction every four weeks from 24 until 32 weeks' gestation, and then every three weeks until birth.
5b.	For pregnant women with SCD with complications (due to SCD or obstetric causes), offer individualized intensive fetal monitoring to guide management, taking into consideration the woman's views and preferences, and the availability of equipment and staff skilled in their use.

Rationale

- In the absence of direct empirical evidence on fetal monitoring for women with SCD, the GDG considered an approach that is woman-centred, based on the ethical principle of autonomy including the importance of informed decision making, and physiological evidence on how SCD might affect the placenta. In pregnant women with SCD with or without complications, antenatal fetal monitoring may help to inform the timing of childbirth.

Remarks

Placentation in SCD

- In a recent study on placentation in SCD (169), of the 72 placentas from women with SCD and pregnancies of more than 20 weeks for which histopathology was available, 50 (69%) had placental pathology and 29 (40%) had maternal vascular malperfusion (MVM). In non-SCD healthy pregnancies, MVM is found in 7–8% of placentas. Outside of SCD, MVM has been linked to conditions associated with placental insufficiency, such as pre-eclampsia. The presence of MVM was associated with adverse pregnancy outcomes (attributable to placental insufficiency), including small for gestational age, iatrogenic preterm birth, and stillbirth. These outcomes were seen in 79% of women with MVM, while the risk of adverse outcomes in a low-risk pregnant population with MVM has been reported at ~47% (170). The study authors proposed that the high rates of MVM observed may suggest that factors inherent in SCD, that remain as yet unidentified, may potentiate the placental disease sometimes present in unaffected healthy women.

Increased risk of small-for-gestational age and stillbirth in women with SCD

- Maternal SCD is associated with increased odds of stillbirth (pooled OR 4.05; 95% CI 2.69 to 6.32; p<0.001), intrauterine growth restriction (pooled OR 2.79, 95% CI 1.85 to 4.21), perinatal mortality (pooled OR 3.76, 95% CI 2.34 to 6.06), and low birthweight (pooled OR 2.00, 95% CI 1.42 to 2.83) (7). These outcomes are consistent across low- and high-income settings (7). The pathophysiology behind these adverse outcomes is multifactorial, but is likely due in part to placental insufficiency.
- Fetal growth restriction (due to any cause) is associated with an increased risk of stillbirth and perinatal death. Outcomes are often dependent on the degree of growth restriction, with the highest risk for fetuses at less than the third percentile or with doppler ultrasound abnormalities. Identification of growth restriction and antenatal fetal surveillance can help predict and prevent stillbirth by informing judgements on the timing of birth.

Type of monitoring

- Depending on the setting, the type of fetal monitoring may include ultrasound, fetal phonocardiogram, one-dimensional Doppler, cardiotocography (including non-stress test, contraction stress test, acoustic stimulation), fetal electrocardiogram and fetal magnetocardiography, at a frequency that is related to the monitoring method and predictive value for stillbirth.

Timing of monitoring

- Modelling to estimate the effect of the interval between examinations on fetal growth restriction in the general pregnant population suggests that taking measurements at least three weeks apart may minimize false positive rates (171). False positive rates were higher when the first scan was performed at 36 weeks (compared to first scan at 32 weeks) (171).

Accuracy of ultrasound in detecting fetal growth restriction

- Over time, there have been several improvements in ultrasound technologies including high-resolution ultrasonography, linear transducer, radiant flow, three-/four-dimensional ultrasound, and artificial intelligence (172). The accuracy of ultrasound estimated fetal weight has improved in the last decade, though a lack of consistency remains evident (173). Key sources of inaccuracy identified in a systematic review included difficulties obtaining accurate fetal measurements in late gestation. The remaining barriers were operator dependent, including lack of experience and insufficient training and audit (173).

Interventions in the context of fetal growth restriction

- There are no proven interventions for small for gestational age and fetal-growth restriction other than birth of the baby. However, identification of fetal-growth restriction can trigger assessment of fetal wellbeing, including discussion of fetal movements and cardiotocography. Maternal assessment can also be offered, including blood pressure and proteinuria assessment.

Adverse effects associated with increased fetal monitoring

- The advantages of fetal monitoring need to be balanced against any potential adverse effects. For example, certain findings may be considered indications for induction. WHO notes that induction of labour can increase the risk of iatrogenic complications (i.e. inadvertent prematurity) and use of resources (i.e. induction agents, health workers, facility preparedness) (174).
- Though antenatal ultrasound is largely seen as positive, long-term adverse psychological and reproductive consequences have been reported for some women (175).

Costs

- The GDG acknowledged the need to consider the cost of fetal monitoring for women, as there may be increased out-of-pocket costs.
- In some low-income settings, access to ultrasound may be limited due to lack of staff and other resources, as well as the costs incurred for women and the distance they would have to travel to attend appointments (175).

3.1.6 Care around birth

Timing of birth

Recommendation — timing of birth

6. When making decisions about the timing of birth (awaiting spontaneous labour or planned birth) for women with SCD, take an individualized approach based on the anticipated balance of the benefits of continuing pregnancy to allow fetal maturation and the risk of maternal and neonatal morbidities associated with continuation of the pregnancy, and the woman's views and preferences.

Rationale

- In light of limited published data that stratifies outcomes of pregnancies in women with SCD by gestational age, and small sample sizes in existing studies, the GDG based its recommendation on physiological understanding of SCD in pregnancy and the ethical principle of autonomy.

Remarks

Placentation in SCD

- In a recent study on placentation in SCD (169), of the 72 placentas from women with SCD and pregnancies of more than 20 weeks for which histopathology was available, 50 (69%) had placental pathology and 29 (40%) had MVM. In non-SCD healthy pregnancies, MVM is found in 7–8% of placentas. Outside of SCD, MVM has been linked to conditions associated with placental insufficiency, such as pre-eclampsia. The presence of MVM was associated with adverse pregnancy outcomes (attributable to placental insufficiency), including small for gestational age, iatrogenic preterm birth, stillbirth. These outcomes were seen in 79% of women with MVM, while the risk of adverse outcomes in a low-risk pregnant population with MVM has been reported at ~47% (170). The study authors proposed that the high rates of MVM observed may suggest factors inherent in SCD, that remain as yet unidentified, may potentiate the placental disease sometimes present in unaffected healthy women.

Early birth in the general pregnant population

- WHO recommends induction of labour for women who are known with certainty to have reached 41 weeks of gestation (*moderate certainty*) (174). Routine induction of labour, for women with uncomplicated pregnancies, at less than 41 weeks is not recommended (*low certainty*) (174).

Decision making about timing of birth in women with SCD

- Decisions about the timing of birth need to reflect all aspects of the woman's pregnancy including other pre-existing conditions and the potential for maternal or neonatal complications such as pre-eclampsia or growth restriction.
- Planned early term birth (between 37 and 38 completed weeks of gestation) may be a consideration when:
  - gestational age can be accurately assessed
  - the facility is sufficiently resourced to provide care for the mother and newborn (including management of labour and birth, and potential maternal or newborn complications).

Factors influencing optimal timing of birth

- The GDG acknowledged that different clinical contexts and individual situations may influence the optimal timing of birth. These include:
  - recurrent acute vaso-occlusive pain crisis at or after 34 weeks' gestation
  - admission for moderate to very severe acute chest syndrome at or after 34 weeks' gestation
  - fetal growth restriction
  - settings where there is limited availability of blood for transfusion or other resources that may be necessary if complications arise post induction.

Areas for further research

- The GDG noted the paucity of evidence and identified the question of sickle-cell pathology on placental and pregnancy physiology, which may inform the optimal timing of birth for women with SCD, as a research priority.

Mode of birth

Recommendation — mode of birth

7. Base decisions about mode of birth for women with SCD on the presence or absence of medical or obstetric indications for caesarean birth, availability of local resources (including those required by women to make informed decisions), as well as the woman's views and preferences. In the absence of medical or obstetric indications for caesarean birth, vaginal birth is preferable.

Rationale

- In the absence of direct empirical evidence on mode of birth in women with SCD, the GDG based its recommendation on evidence derived from general pregnant populations and the physiological understanding of SCD and pregnancy.

Remarks

Caesarean birth in the general pregnant population

- WHO concludes that caesarean sections are effective in saving maternal and infant lives, but only when they are required for medically indicated reasons (176). Caesarean sections can cause significant and sometimes permanent complications, disability or death, particularly in settings that lack the facilities and/or capacity to properly conduct safe surgery and treat surgical complications (176).

Caesarean birth in women with SCD

- The systematic review conducted to inform this guideline found that the effect of caesarean section compared to vaginal birth on maternal death, stillbirth and neonatal death is uncertain (one cross-sectional study; 255 women; *very low certainty*) (44).
- The GDG acknowledged that there is insufficient evidence to support pre-labour caesarean birth in women with SCD.

Decision making about mode of birth

- The GDG acknowledged the need to balance the interaction between the pathophysiological mechanisms of SCD and the management of birth (i.e. anaemia and risks associated with haemorrhage; pain, dehydration and risk of precipitating sickle-cell crises).
- Qualitative evidence based on the views of healthy pregnant women (177) (largely from HICs [76%] but including views from women in upper-middle income [13%] and LICs [11%]) suggests that if women have a preference for caesarean birth, the factors underlying this preference include: a strong fear of pain and injuries to the mother and baby during labour and birth (*high confidence*)**;** and positive views on caesarean birth based on qualities associated with better organization and control of the birth process (high confidence).

Trial of labour after caesarean birth

- The GDG did not find any evidence on trial of labour after caesarean (TOLAC) in women with SCD. Consideration of TOLAC in this population will be informed by obstetric indications and availability of local resources.
- The GDG acknowledged the need for clinical judgement and shared decision making, with reference to local protocols, with regard to undertaking TOLAC in women with SCD.

Areas for further research

- The GDG noted the paucity of evidence and identifies the question of the optimal mode of birth for women with SCD as a research priority.

3.1.7 Interpregnancy management

Recommendation — interpregnancy care

8a. Offer women with SCD in the immediate postnatal period and up to six weeks after childbirth care in addition to that outlined in *WHO recommendations on maternal and newborn care for a positive postnatal experience* (28):

- to manage and treat SCD and its complications, using evidence-based interventions including disease-modifying agents such as hydroxycarbamide (hydroxyurea) and pain-management strategies;
- to prevent morbidities such as thrombotic events by considering the need for, and initiating, thromboprophylaxis, as per local recommendations;
- to guide choice of contraceptive methods;
- to screen the newborn for SCD; and
- to guide counselling on the safety of breastfeeding for the baby.

Recommendation for health service programmes

8b. For women with SCD, integrate care across the life course, including sexual and reproductive health care, with specialized disease care, which may include: supporting optimal health and well-being; providing pre-pregnancy counselling and guidance on pregnancy planning; and optimizing treatment across and beyond the reproductive continuum.

Rationale

- In the absence of direct empirical evidence to support recommendations on specific interventions for women with SCD in the interpregnancy period, the GDG based its recommendations on physiological understanding of SCD in the postnatal period, periconceptually, and in women of reproductive age.

Remarks

Conceptual approach

- The GDG noted that the interpregnancy phase cannot be defined prospectively. Beginning from the time of birth / termination of pregnancy, it extends beyond the initial six weeks after birth. To support health throughout the reproductive continuum and in the interests of inclusivity, all women of reproductive age who have been pregnant may be considered to be in the 'interpregnancy' period, unless they have undergone menopause or taken steps to permanently avoid pregnancy.
- After the initial postnatal period, women need to be transitioned back to specialized care for SCD. When the woman is cared for by a multidisciplinary team during pregnancy, this transition will likely be straightforward and is a fundamental rationale for "integrated" care in and outside of pregnancy. The GDG acknowledged that these care systems may not exist, may be inadequately organized, or remain aspirational in many settings. At a minimum, referral systems and mechanisms need to be in place to communicate a woman's pregnancy and postnatal course to her general care providers, including those managing her SCD.
- Although most women with SCD will have had previous contact with health-care facilities to manage the condition, the postnatal period (immediate and beyond) may provide additional opportunities for "catch up care", such as ensuring up-to-date immunization.

Risks in the early postnatal period

- The immediate postnatal period (i.e. in the first week postnatally) is often when complications occur.
- Women with SCD have an increased risk of severe maternal morbidity compared to women without SCD (178). In addition, women in active vaso-occlusive crisis at the delivery admission have an approximately nine-fold higher risk of severe maternal morbidity up to 42 days' post-discharge compared with women with SCD not in crisis at the delivery admission (178).
- Women with SCD have an increased risk of VTE compared to the general population (see 'Thromboprophylaxis in pregnant women with uncomplicated SCD'; page 26). In the immediate postnatal period, this risk may be further magnified especially in the context of decreased mobility, following a caesarean birth, or if the woman has a history of VTE.

Contraception

- The *WHO medical eligibility criteria wheel for contraceptive use* (179) suggests that for women with SCD, progestogen-only pills, progestogen-only injectables, implants, and levongestrel-releasing intrauterine devices can all be used in any circumstance; and that combined hormonal contraceptives and copper intrauterine devices can be suggested on a case-by-case basis. The availability of each method, however, may vary depending on context, and local guidelines may also provide specific guidance. The GDG also noted that copper intrauterine devices may increase bleeding in the first three months of use.

- Decisions on contraception need to be tailored to the individual women, taking into account the woman's preferences and noting that these may change over time.

Care for the newborn

- Guidance from the WHO African Region supports systematic newborn screening for SCD if available (23). Integration of newborn screening into existing primary health-care immunizations has been shown to be feasible in settings with limited resources (180). Point-of-care screening tests have been shown to provide an affordable, reliable, and easy-to-use method to screen for SCD, ensuring the earliest diagnosis possible, the highest level of follow-up of participants, access to treatments locally (including penicillin prophylaxis, pneumococcal vaccinations, and hydroxycarbamide) and effective prevention procedures regionally (e.g. transcranial doppler for risk of stroke) (180).

Medications while breastfeeding

- *Pain medications:* Paracetamol and NSAIDs are considered safe during breastfeeding.
- *Hydroxycarbamide:* Breastfeeding has typically been avoided for women with SCD receiving hydroxycarbamide therapy, despite sparse pharmacokinetics data. In a recent study (n=16) hydroxycarbamide transferred into breastmilk with a relative infant dosage of 3.4%, which is below the recommended 5–10% safety threshold (181).
- Counselling for women on the safety of breastfeeding for the baby needs to include what is known about the transfer of hydroxycarbamide to the baby and the strength of the evidence. Such counselling aims to enable the woman to be a part of a shared decision-making process involving the woman and her health care providers. In addition to the woman herself, members of that decision-making group may include obstetricians, midwives, paediatricians and specialist SCD care providers).

4 Dissemination and implementation of the guideline

The dissemination and implementation of this guideline is to be considered by all stakeholders involved in the provision of care for pregnant women at the international, national and local levels. There is a vital need to increase women's access to maternal health care, and strengthen the capacity at health care facilities of all levels to ensure they can provide high-quality services to all women giving birth. It is therefore crucial that the guideline recommendations be translated into care packages and programmes at country and health-care facility levels, where appropriate. In particular, the recommendations will need to be incorporated into existing programmes and policies on the management of SCD in pregnancy and childbirth.

4.1 Dissemination and evaluation

An executive summary containing the recommendations, remarks, implementation considerations and research priorities will be prepared for public dissemination. The WHO Steering Group will also develop derivative tools to aid understanding and adaptation of these recommendations to local contexts.

The recommendations and derivative tools will be disseminated through WHO regional and country offices, ministries of health, professional organizations, WHO collaborating centres, other United Nations agencies and nongovernmental organizations, among others. The recommendations will be published on the WHO Department of Sexual and Reproductive Health and Research website and promoted in the quarterly HRP News disseminated to over 8000 subscribers, including clinicians, health programme managers, policy-makers, researchers and service users from all around the world. Updated recommendations are also routinely disseminated during meetings and scientific conferences attended by WHO maternal and perinatal health staff.

The executive summary and recommendations from this publication will be translated into the six official United Nations languages for dissemination through the WHO regional and country offices and during meetings organized by, or attended by, staff of the WHO Department of Sexual and Reproductive Health and Research and the Department of Maternal, Newborn, Child and Adolescent Health. Technical assistance will be provided to any WHO regional office willing to translate these recommendations into any of their languages. In addition, the publication of journal articles presenting the recommendations and key implementation considerations will be considered in compliance with WHO's open access and copyright

policies. Relevant WHO clusters, departments and partnerships, such as the Partnership for Maternal, Newborn and Child Health (PMNCH), will also be part of this dissemination process.

In order to ensure these recommendations have a positive impact on maternal and perinatal health at the country level, coordinated action between international agencies, national departments of health and key maternal and perinatal health stakeholders is needed. National and subnational working groups should assess current national guidelines and protocols, and determine whether development of new guidelines or updating of existing guidelines is required in line with these new WHO recommendations. WHO staff at the headquarters, regional and country levels, as well as international agency partners and international professional societies (such as FIGO and ICM), and national professional associations, can support national stakeholders in developing or revising existing national guidelines or protocols, and optimizing their implementation.

In the context of humanitarian emergencies, the adaptation of the current recommendations should consider their integration and alignment with other response strategies. Additional consideration of the unique needs of women in emergency settings, including women's values and preferences, should be made. Context-specific tools and toolkits may be required in addition to standard tools to support the implementation of the recommendation in humanitarian emergencies.

4.2 Implementation considerations

As part of the recommendation development process, implementation considerations were developed. These may assist policy-makers, clinicians and other stakeholders to better prepare for implementation.

- The successful introduction of evidence-based policies related to the management of chronic medical conditions such as SCD into the pregnancy care model will depend on well-planned, participatory and consensus-driven processes of integration and implementation. These processes may include the development or revision of national guidelines or protocols based on these recommendations, and engagement with all relevant stakeholder groups, including skilled health-care providers. Modifications to the recommendations, if necessary, should be made with justification and documented in an explicit and transparent manner. The Department of Sexual and Reproductive Health and Research and the Department of Maternal, Newborn, Child and Adolescent Health (WHO) will support national and subnational groups to adapt and implement the recommendations based on existing strategies.
- Implementation of the recommendations for the management of SCD in pregnancy must be considered within the broader context of ensuring that all women have access to respectful, woman-centred care throughout their life course.
- National health systems must support an enabling environment for the implementation of these recommendations, including education to support behaviour change among skilled health personnel teams to facilitate the use of evidence-based practices. Clear and up-to-date clinical protocols should be available to skilled health-care providers regarding the care of medical conditions in pregnancy.
- Local professional societies and training institutions can have an important role in implementation. An all-inclusive and participatory process should be encouraged.

- National health systems must ensure that supplies of medicines and commodities (including blood for transfusion) are available in health-care facilities where childbirth services are provided. These resources must be safe, legitimate and manufactured according to good manufacturing practices. To ensure that the resources are of high quality, robust and sustainable regulatory, procurement and logistics processes must be established, ensuring that good-quality products are obtained, transported and stored correctly.
- Skilled health-care providers working in settings where women give birth will require training and supportive supervision on how to integrate the care of chronic medical conditions into routine pregnancy care, and how to inform and counsel women, as appropriate. In settings where a new practice is introduced (or where recommended practices are changed), additional training and monitoring may be required. In contexts with high rates of personnel turnover, pre-service training and regular opportunities for ongoing training and competency assessment are particularly important.
- Consideration should be given to which health-care providers have prescription and administration authority for medications to treat SCD, and whether this is reflected in their scope of practice.

4.3 Anticipated impact on the organization of care and resources

Effective implementation of the recommendations in this guideline may require reorganization of care and redistribution of health-care resources, particularly in low- and middle-income countries. The GDG noted that updating training curricula and providing training on the recommendations would increase their impact and facilitate their implementation.

As part of efforts to implement these recommendations, health system stakeholders may wish to consider the following potential barriers to their application:

- feasibility of components of the recommendations, barriers and facilitators to their implementation;
- lack of human resources with the necessary knowledge of the condition, and its inheritance patterns;
- lack of human resources with the requisite expertise and skills to implement, supervise and support recommended practices;
- lack of infrastructure and multidisciplinary teams to support interventions;
- lack of resources for active implementation strategies;
- lack of essential equipment, supplies and medicines;
- lack of health information management systems designed to document and monitor recommended practices (e.g. patient records, registers);
- lack of consistent staffing from high provider turnover impacting the sustainability and scalability of interventions.

4.4 Monitoring and evaluating guideline implementation

The implementation and impact of these recommendations will be monitored at the health service, country and regional levels, as part of broader efforts to monitor and improve the quality of maternal and newborn care. The WHO document *Standards for improving quality of maternal and newborn care in health facilities* (182) provides a list of prioritized input, output and outcome measures that can be used to define quality of care criteria and indicators and that should be aligned with locally agreed targets. In collaboration with the monitoring and evaluation teams of the WHO Department of Sexual and Reproductive Health and Research and the WHO Department of Maternal, Newborn, Child, Adolescent Health and Ageing, data on country- and regional-level implementation of the recommendations will be collected and evaluated in the short to medium term to assess their impact on national policies of individual WHO Member States. Interrupted time series could be used to obtain the relevant data on the use of interventions contained in this guideline.

5 Research implications

The GDG identified important knowledge gaps directly related to the PICO questions, or which may have a direct impact on the implementation of these recommendations. The following areas were identified as priority questions for high-quality evidence generation, especially in settings of high prevalence:

- folic acid supplementation among pregnant women with SCD taking intermittent preventive treatment with sulfadoxine-pyrimethamine;
- the risks and benefits of prophylactic transfusion, as well as the best timing, frequency and thresholds used and comparisons between simple, manual exchange and automatic exchange transfusions;
- the effect of hydroxycarbamide and other disease-modifying agents in pregnancy on maternal and fetal/neonatal outcomes;
- qualitative studies relating to women's informed consent and experiences of hydroxycarbamide;
- optimal methods of pain management in the antenatal period — specifically around the use of medications;
- thromboprophylaxis for non-hospitalized women;
- intravenous fluids for pregnant women with SCD hospitalized with vaso-occlusive crisis, including the type and volume of fluid;
- the most effective thromboprophylaxis schedule for women who are hospitalized with SCD;
- outcomes of pregnancies in women with SCD stratified by gestational age at birth;
- the effect of sickle-cell pathology on placental and pregnancy physiology, which may inform the optimal timing of birth for women with SCD;
- optimal timing of postnatal visits (e.g. one week compared to six weeks);
- the safety of hydroxycarbamide use during lactation for the infant and the impact of its use on infant feeding choices;
- the optimal mode of contraception.

6 Updating the recommendations

The Maternal and Perinatal Health Guideline Technical Advisory Group convenes regularly to review WHO's current portfolio of maternal and perinatal health recommendations and to help WHO prioritize new and existing questions for recommendation development and updating. These recommendations will be included in those reviews. In the event that new evidence that could potentially impact the current evidence base is identified, these recommendations may be updated. If no new reports or information is identified, the recommendations may be revalidated.

WHO welcomes suggestions regarding additional questions for inclusion in the updated recommendations. Please email your suggestions to srhmph@who.int.

Annex 1.
External experts and WHO staff involved in the preparation of the recommendations

Guideline development group

Bosede AFOLABI (Chair)
Professor of Obstetrics and Gynecology
College of Medicine
University of Lagos
Lagos, Nigeria

Tamima ALDUGHAISHI
Senior Consultant Maternal Fetal Medicine
Sultan Qaboos University Hospital
Muscat, Oman

Monika ASNANI
Professor of Family Medicine and Epidemiology
Sickle Cell Unit- Caribbean Institute for Health Research
The University of West Indies
Mona Campus, Jamaica

Eugenia Vicky ASARE
Senior Specialist Haematology
Ghana Institute of Clinical Genetics
Korle-Bu Teaching Hospital
Accra, Ghana

Ochuwa BABAH
Senior Lecturer of Obstetrics and Gynecology
College of Medicine
University of Lagos
Lagos, Nigeria

Lea Kilenga BEY
Executive Director
Africa Sickle Cell Organization
Nairobi, Kenya

Harriet BIRUNGI
Vice President
International Programs Division
Population Council
Nairobi, Kenya

Rodolfo CANCADO
Hematology
Faculdade de Ciencias Medicas da Santa Casa de São Paulo
São Paulo, Brazil

John EHIRI
Professor of Health Promotion Sciences Senior Associate Dean for Academic Affairs
University of Arizona
Arizona, United States of America

Laure JOSEPH
Hematology
Département de Biothérapie Hôpital Necker-Enfants Malades
Paris, France

Isaac ODAME
Professor
Departments of Medicine and Paediatrics, Division of Haematology/Oncology
The Global Sickle Cell Disease Network Centre for Global Child Health
The Hospital for Sick Children
Toronto, Canada

Eugene OTENG-NTIM
Professor
Department of Women and Children's Health, School of Life Course and Population Sciences, King's College,
London, United Kingdom of Great Britain and Northern Ireland

Wendy POLLOCK
Associate Professor
School of Nursing and Midwifery
Monash University
Melbourne, Australia

Partner organizations/observers

International Federation of Gynecology and Obstetrics (FIGO)
Diana RAMASAUSKAITE
Akaninyene Eseme Bernard UBOM

International Pediatric Association (IPA)
Nita RADHAKRISHNAN

NCD Alliance
Mychelle FARMER

United Nations Childrens Fund (UNICEF)
Raoul BERMEJO

United States Agency for International Development (USAID)
Meridith MIKULICH

Guideline methodologists

Jen RAMSON
Consultant

Myfanwy WILLIAMS
Consultant

Evidence synthesis group

Kelli BARBOUR
Assistant Professor Maternal Fetal Medicine and Global Women's Health
Baylor College of Medicine and
Texas Children's Hospital
Texas, United States of America

Sarah BOUDOVA
Fellow, Maternal Fetal Medicine
Thomas Jefferson University
Pennsylvania, United States of America

La'Ron BROWNE
St Jude Hospital
Tennessee, United States of America

Soo DOWNE
Professor
THRIVE Centre
University of Central Lancashire
School of Community Health and Midwifery
Lancashire, United Kingdom of Great Britain and Northern Ireland

Kenneth FINLAYSON
Research Associate
University of Central Lancashire
School of Community Health and Midwifery
Lancashire, United Kingdom of Great Britain and Northern Ireland

Yaneve FONGE
Fellow, Maternal Fetal Medicine
UPMC Magee-Women's Hospital
Pennsylvania, United States of America

Apiwat JONGJAKAPUN
Department of Obstetrics and Gynecology
Faculty of Medicine
Khon Kaen University
Khon Kaen, Thailand

Jenny JUNG
Maternal, Child and Adolescent Health Program
Burnet Institute
Melbourne, Australia

Nampet JAMPATHONG
Cochrane Thailand Khon Kaen University
Khon Kaen, Thailand

Pisake LUMBIGANON
Professor
Faculty of Medicine Convenor, Cochrane Thailand
Director, WHO Collaborating Centre for Research Synthesis in Reproductive Health
Faculty of Medicine Khon Kaen University
Khon Kaen, Thailand

Chetta NGAMJARUS
Associate Professor
Department of Epidemiology and Biostatistics,
Faculty of Public Health,
Khon Kaen University,
Khon Kaen, Thailand

Porjai PATTANITTUM
Associate Professor
Department of Epidemiology and Biostatistics
Faculty of Public Health
Khon Kaen University
Khon Kaen, Thailand

Beth PINELES
Assistant Professor of Obstetrics and Gynecology
Hospital of the University of Pennsylvania
Pennsylvania, United States of America

Jen SOTHORNWIT
Assistant Professor
Department of Obstetrics and Gynecology
Faculty of Medicine
Khon Kaen University
Khon Kaen, Thailand

Termtem WAIDEE
Department of Obstetrics and Gynecology
Faculty of Medicine
Khon Kaen University
Khon Kaen, Thailand

WHO country and Regional offices

Bremen DE MUCIO
Maternal Health Regional Advisor (CLAP)

Pablo DURÁN
Regional Adviser on Perinatal Health

Karima GHOLBZOURI
Regional Adviser for Sexual and Reproductive Health & Research

C. Anoma JAYATHILAKA
Acting Director
Medical Officer
Family Health, Gender and Life Course

Shogo KUBOTA
Coordinator
Maternal Child Health and Quality Safety

Oleg KUZMENKO
Technical Officer
(Sexual and reproductive health focal point)
Reproductive Health
Division of Country Health Policies and Systems

Priya MANNAVA
Technical Officer
Maternal Child Health and Quality Safety

Léopold OUEDRAOGO
Regional Adviser
Reproductive, Maternal Health and Ageing

WHO steering group

Prebo BARANGO
Cross-cutting Specialist
NCDs and Special Initiatives
Department of Noncommunicable Diseases

Maria BARREIX ETCHEGOIMBERRY
Technical Officer
Maternal and Perinatal Health
Department of Sexual and Reproductive Health and Research

Doris CHOU
Medical Officer
Maternal and Perinatal Health
Department of Sexual and Reproductive Health and Research

Ayesha DE COSTA
Scientist
Department of Maternal, Newborn, Child and Adolescent Health and Ageing

Maria Nieves GARCIA CASAL
Scientist
Department of Nutrition and Food Safety

Olufemi OLADAPO
Unit Head
Maternal and Perinatal Health
Department of Sexual and Reproductive Health and Research

Roberta ORTIZ SEQUEIRA
Medical Officer
Department of Noncommunicable Diseases

Lisa ROGERS
Technical Officer
Department of Nutrition and Food Safety

Meera UPADHYAY
Medical Officer
Department of Maternal, Newborn, Child and Adolescent Health and Ageing

External review group

A. Kinga MALINOWSKI
Associate Professor
Maternal-Fetal Medicine
Mount Sinai Hospital
Toronto, Canada

Bertha MASEKO
Maternal Health Group Manager
Malawi Liverpool Wellcome Programme
Blantyre, Malawi

Babasola OKUSANYA
Associate Professor
Obstetrics and Gynecology at College of Medicine
University of Lagos
Lagos, Nigeria

Lydia PECKER
Associate Professor
John Hopkins School of Medicine
Baltimore, United States of America

Annex 2.
Priority outcomes used in decision making

WHO outcomes included for all PICOs

Critical maternal outcomes

- Maternal death
- Maternal functioning and well-being
- Women's views and experiences

Important maternal outcomes

- Antenatal hospitalization
- Admission to intensive care
- Mode of birth

Critical newborn outcomes

- Stillbirth/fetal death
- Neonatal death
- Perinatal death

Important newborn outcomes

- Admission to neonatal intensive care
- Gestational age at birth
- Preterm birth (<32 weeks; <37 weeks)
- Birthweight
- Intrauterine growth restriction
- Low birthweight (<2500 g)
- Small-for-gestational age (<10th centile for gestational age)
- Apgar score of less than seven at five minutes
- Neurodevelopmental outcomes (into infancy and childhood)

Health service outcomes

- Antenatal admissions to hospital for the woman and length of stay
- Emergency department visits for the woman
- Admission to intensive care unit for the woman
- Length of postnatal hospitalization for the woman
- Length of neonatal hospitalization
- Costs of care for the woman or baby or both

Priority outcomes for individual PICOs

Maternal outcomes

- Antepartum haemorrhage
- Caesarean section
- Cerebrovascular accident
- Hypertensive disorders of pregnancy
- Identification of causes of anaemia
- Induction of labour
- Iron overload
- Lower respiratory tract infection (bronchitis, pneumonia)
- Malaria infection
- Maternal postnatal infection
- Postpartum haemorrhage
- Pyelonephritis
- SCD crisis (pain/vaso-occlusive, acute chest syndrome, aplastic, splenic sequestration)
- Sepsis
- Thrombotic events
- Uptake of genetic testing

Newborn outcomes

- Fetal diagnosis
- Neonatal SCD
- Miscarriage
- Congenital anomaly
- Fetal growth restriction

Annex 3. Summary and management of declared interests from GDG members

Name and title	Expertise contributed to guideline development	Declared Interest	Management of declared interest
Guideline development group			
Bosede AFOLABI	Content expert and end user (obstetrics)	Received funding from the TETFund, Nigeria as co-investigator on the PIPSICKLE trial; received an honorarium to speak at a conference (under 2000 USD)	The expert was recused from developing recommendations related to the intervention in the PIPSICKLE trial. This declared conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility
Tamima ALDUGHAISHI	Content expert and end user (obstetrics)	None declared	Not applicable
Eugenia Vicky ASARE	Content expert and end user (haematology)	None declared	Not applicable
Monika ASNANI	Content expert and end user (public health)	Participated in a Working Group on measures for phenotypes and exposures	Not applicable

Name and title	Expertise contributed to guideline development	Declared Interest	Management of declared interest
Ochuwa BABAH	Content expert and end user (obstetrics)	Received funding from the TETFund, Nigeria as co-investigator on the PIPSICKLE trial	The expert was recused from developing recommendations related to the intervention in the PIPSICKLE trial. This declared conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility
Lea Kilenga BEY	Community and stakeholder perspective	Founded and acts as CEO of Africa Sickle Cell Organization	This declared conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility
Harriet BIRUNGI	Content expert and end user (gender and rights)	None declared	Not applicable
Rodolfo CANÇADO	Content expert and end user (obstetrics)	None declared	Not applicable
John EHIRI	Content expert and end user (public health)	None declared	Not applicable
Laure JOSEPH	Content expert and end user (haematology)	Received honorarium fees for consulting activities and travel to conferences (The honorarium received were under 2000 USD)	This declared conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility
Isaac ODAME	Content expert and end user (haematology)	Received funding for a research project on point of care testing for sickle cell disease	Not applicable

Name and title	Expertise contributed to guideline development	Declared Interest	Management of declared interest
Eugene OTENG-NTIM	Content expert and end user (obstetrics)	Received funding for a feasibility trial on prophylactic exchange blood transfusion versus standard care (in sickle cell)	The expert was recused from developing recommendations related to the intervention (transfusions). This declared conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility
Wendy POLLOCK	Content expert and end user (obstetrics)	None declared	Not applicable
Guideline methodologists			
Jen RAMSON	Evidence synthesis, guideline methodology	None declared	Not applicable
Myfanwy WILLIAMS	Evidence synthesis, guideline methodology	None declared	Not applicable
Evidence synthesis group			
Kelli BARBOUR	Evidence synthesis	None declared	Not applicable
Sarah BOUDOVA	Evidence synthesis	None declared	Not applicable
La'Ron BROWNE	Evidence synthesis	None declared	Not applicable
Soo DOWNE	Evidence synthesis	None declared	Not applicable
Kenneth FINLAYSON	Evidence synthesis	None declared	Not applicable
Yaneve FONGE	Evidence synthesis	None declared	Not applicable
Nampet JAMPATHONG	Evidence synthesis	None declared	Not applicable
Apiwat JONGJAKAPUN	Evidence synthesis	None declared	Not applicable

Name and title	Expertise contributed to guideline development	Declared Interest	Management of declared interest
Jenny JUNG	Evidence synthesis	None declared	Not applicable
Pisake LUMBIGANON	Evidence synthesis	None declared	Not applicable
Chetta NGAMJARUS	Evidence synthesis	None declared	Not applicable
Porjai PATTANITTUM	Evidence synthesis	None declared	Not applicable
Beth PINELES	Evidence synthesis	None declared	Not applicable
Jen SOTHORNWIT	Evidence synthesis	None declared	Not applicable
Termtem WAIDEE	Evidence synthesis	None declared	Not applicable
Observers			
Raoul BERMEJO	United Nations partner		
Mychelle FARMER	Observer - Civil society organization	None declared	Not applicable
Meridith MIKULICH	Observer - implementing agency	None declared	Not applicable
Nita RADHAKRISHNAN	Observer - professional organization	None declared	Not applicable
Diana RAMASAUSKAITE	Observer - professional organization	None declared	Not applicable
Akaninyene Eseme Bernard UBOM	Observer - professional organization	None declared	Not applicable

Name and title	Expertise contributed to guideline development	Declared Interest	Management of declared interest
External review group			
A. Kinga MALINOWSKI	Content expert and end user (obstetrics)	Received research funds for a study looking at risk factors for adverse outcomes in pregnant individuals with SCD	This is not considered significant to preclude external review of the guideline.
Bertha MASEKO	Content expert and end user (obstetrics)	None	Not applicable
Babasola OKUSANYA	Content expert and end user (obstetrics)	None	Not applicable
Lydia PECKER	Content expert and end user (hematology)	Received research funds for a study looking at risk factors for adverse outcomes in pregnant individuals with SCD	This is not considered significant to preclude external review of the guideline.

Web Annex

Evidence-to-decision frameworks.

Available here, https://doi.org/10.2471/B09416.

Web Annex Section	Comparison
1.0	Medication management for pregnant women with SCD
2.0	Pain management for pregnant women with SCD
3.0	Fluid-management plans for pregnant women hospitalized with SCD
4.0	Thromboprophylaxis for pregnant women hospitalized with SCD
5.0	Additional fetal monitoring for pregnant women with SCD
6.0	Timing of delivery for pregnant women with SCD
7.0	Mode of birth for pregnant women with SCD
8.0	Interpregnancy management for postnatal women with SCD

White paper

Jung J., et al. Additional care during pregnancy for women with sickle cell disease (SCD). Available here, https://who.canto.global/b/LIVKQ-

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World Health Organization
Department of Sexual and Reproductive Health and Research
20 Avenue Appia
1211 Geneva 27
Switzerland
Email: srhhrp@who.int
Website: https://www.who.int/teams/sexual-and-reproductivehealth-and-research-(srh)/
www.who.int