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Review Article

Current Issues and Options for Hormonal Contraception in Adolescents and Young Adult Women With Sickle Cell Disease: An Update for Health Care Professionals

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Abstract. Women with sickle cell disease (SCD) are of particular concern regarding the significantly increased risk of pregnancy-related morbidity, mortality, and adverse outcomes. They have limited knowledge of pregnancy and childbirth risks, as well as of the benefits and risks of contraceptives. Thus, there is an urgent need for appropriate information about reproductive family planning to reduce unintended pregnancy. Any decision regarding the use of contraceptives has to be based on the efficacy and risk/benefit ratio of the method used. Both the World Health Organization (WHO) and the Centers for Disease Control (CDC) have developed, published, and updated evidence-based guidelines for medical providers for the use of contraceptives in patients with specific medical chronic conditions. This article provides an overview of the present knowledge on the use of contraceptives in women with SCD. We believe that the collaboration between health care professionals (hematologists, obstetricians, endocrinologists, and primary care providers) can play a major role in identifying the safer contraceptive method to abolish the risks of unintended pregnancy and preserve the health status of patients with SCD.

Keywords: Sickle Cell Disease; Pregnancy; Contraception; Recommendations.

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Introduction. Sickle cell disease (SCD) represents one of the most common monogenic blood disorders worldwide, with an incidence of over 300,000 newborns affected annually, two-thirds of whom are in Africa.[1-3] Owing to population migration, SCD is now an increasing health problem worldwide with increasing numbers of affected individuals in Europe.[4]

The term SCD refers to a set of disorders characterized by the inheritance of the structural HbS variant. When the HbS or sickle cell variant is inherited

in a homozygous state (HbSS) it is defined as sickle cell anaemia; however, it is usually clinically silent when inherited in a heterozygous form (HbAS). SCD complex also includes compound heterozygotes disorders in which the HbS variant is coinherited with another hemoglobinopathy, e.g. ß-thalassemia heterozygotes (HbS/ß^0-thal, HbS/ß$^+$-thal and HbS/(δβ)^0-thal) known as microdrepanocytic disease, or with other ß-globin structural variants.[5]

Patients with HbSS, HbSC, HbSD or HbS/ß^0 disease lack normal β-globin chains, and so they have no HbA. In HbSS, the HbS levels are usually above 80%. The HbF levels are usually increased up to 20%; high HbF levels are negatively related to the severity of clinical symptoms. The presence of HbA and increased HbF in patients with HbS/β$^+$ thal ameliorate the clinical symptoms of patients and in particular the obstructive and hemolytic crises.[1,2,5]

HbSS and HbS/ß^0-thal disease have identical hematological phenotypes and the most severe clinical and hematological phenotypes, but in both cases, the clinical severity varies markedly. HbS/ß$^+$-thal presents with a broader clinical spectrum depending on the severity of the mutation of the ß -thalassemia gene and the levels of HbA.

SCD is associated with chronic activation of coagulation and with an increased risk for venous thrombosis. The phenotypic variation in SCD is thought to be related to a complex interaction between hemolysis, vaso-occlusion, endothelial dysfunction, and hyperviscosity.[1,2] Patients with SCD suffer from a variety of clinical events due to small and large vessels occlusion, including vaso-occlusive painful episodes, strokes, and acute chest syndrome.[6] Such episodes may be associated with derangements of plasma and cellular haemostatic mechanisms that may impart a thrombophilic tendency.[6] Reported changes include an increase in thrombin generation, platelet activation and decreased levels of circulating anticoagulants such as protein C and S.[7]

In addition, venous thromboembolism (VTE), which includes both deep vein thrombosis and pulmonary embolism, is increasingly recognized as a critical complication of SCD resulting from the hypercoagulable state that is elicited by the disease. It has been described in children and adults with SCD,[8,9] HbS/ß$^+$-thalassemia[10] and sickle cell trait.[8,11,12]

By the age of 30 years, up to 25% of patients with SCD experience ≥ 1 episode of VTE.[13,14]

Splenectomy, which is a known risk factor for VTE in other hemoglobinopathies such as β-thalassemia intermedia and major has also been associated with VTE and in sickle cell variant syndrome of microdrepanocytic disease.[10,14]

Information on contraception in women with SCD is limited.[15-18] The course of SCD can be worsened by pregnancy which is associated with high rates of maternal morbidity despite advances in management. Pregnancy is associated with an increased incidence of painful episodes, infection, pulmonary complications, VTE, antepartum bleeding, and increased risk of pre-eclampsia.[19-21] Because of this, pregnancy should be timed during a period of relative disease stability, although this may prove impossible as the disease is unpredictable in its course. Therefore, appropriate consultation both for pregnancy planning and effective contraception is of paramount importance.[22]

In normal females, the synthetic steroids used in contraception induce metabolic changes on lipoprotein, insulin response to glucose and coagulation factors, all of which have been associated with cardiovascular and venous thrombosis. VTE is a rare event in normal women of reproductive age, and its incidence increases with age.[23] In recent reviews and meta-analysis studies, an increased risk has been demonstrated in users of combined hormonal contraceptives (COCs) containing ethinylestradiol (EE) and different progestins.[24,25] Although the risk is increased approximately 4-fold as compared with non-users, the absolute risk is low (about 7/10,000 women-years) and lower than the risk of pregnancy.[26]

The main objective of this article is to provide a brief overview of the present knowledge of the available options for hormonal contraception in adolescent and young adult women with SCD and consider the current risk-benefit analysis of available contraceptive methods.

A. Clinical Implications and Hormonal Contraception in General Practice. Patients with SCD seen in haematology practice are generally clinically heterogeneous with a spectrum of clinical findings and symptoms.

For an appropriate decision, women with SCD should be provided with up-to-date research-based evidence regarding suitable methods for hormonal contraception and be referred (if needed) to a contraceptive specialist for further advice. Adolescents (males and females) with SCD should be allowed to privately discuss their family planning needs and receive care in the context of the relevant law.[27]

Before prescribing any contraceptive method, a careful history of past and present medical conditions, drugs use, and family history, followed by physical examination and laboratory assessment is required to exclude conditions or risk factors that might be a contraindication to contraceptive use.

Specifically, information regarding migraine, risk factors for cardiovascular disease (smoking, hypertension, obesity, glucose intolerance, dyslipidemia, thrombophilia, previous VTE), blood pressure measurement and body mass index (BMI) are essential. A pregnancy test ensures the initiation of contraception before pregnancy.

Patients also require reliable information on the correct use of the pill, together with detailed information on how to avoid sexually transmitted diseases (STDs) by combining pill use with a condom.[28] Discussion about emergency contraception should occur at each visit when providing anticipatory guidance strategies regarding safe sex practices.

B. Overview of Hormonal Contraceptive Choices. Globally, it has been recognised that adolescents and young women with SCD are at high risk of unintended pregnancy. In a study, only 33% of a group of women with SCD used any form of contraception compared to 66% in the control group.[18]

When choosing a hormonal contraceptive method, it is important to recognize the distinct advantages and disadvantages of each method and consider the following factors: efficacy, ease of dosing/duration of action, impact on menstrual bleeding, time to return to fertility, side effects, cost, non-contraceptive benefits, and medical contraindications. The products, utilized to inhibit conception, exert their contraceptive actions at the levels of ovarian-produced hormones or block the sperm from fertilizing the egg.

Non-hormonal barrier and behavioural methods include male and female condoms, diaphragms, caps, shields, intrauterine devices (IUDs), spermicides, withdrawal, fertility awareness and natural family planning.

a. Short-acting Reversible Contraception (SARC) methods include two main groups: the combined hormonal contraceptives (COCs) with estrogen and progestin components and the progestin-only pills (POPs).

Contraceptive action is provided by: (a) ovulation suppression by inhibiting follicle-stimulating hormone (FSH) and luteinizing hormone (LH); (b) cervical mucosal changes that inhibit sperm penetration; and (c) endometrial changes that reduce the chances of successful implantation.[29,30]

1. Combined hormonal contraceptives (COCs) include the following methods:

- Oral
- Transdermal patches
- Vaginal rings

Combined oral contraceptives (COCs) remain the most frequently prescribed form of contraception.

The majority of COCs contains ethinylestradiol (EE) as the estrogen component. There are a considerable number of different combinations of COCs concerning both compounds and doses. COCs vary in dose and type of estrogen, dose and type of progestin, regime (monophasic, biphasic, triphasic or quadriphasic) and route of administration (oral, patch, vaginal ring or subcutaneous implant). The prescription pattern differs between different parts of the world.

The estrogen content of the COCs ranges from 15 to 50 µg per active tablet. Although EE and estradiol are the only estrogens used in COC, many progestins are currently available. Their content varies considerably dependent upon the potency differences in the compound used.

Two of the newer progestogens, (desogestrel and gestodene) have been associated with a small increase in the risk of venous thromboembolism. In the late 1980s, three new "third-generation" progestogens were introduced (norgestimate, desogestrel and gestodene) which were designed to have less androgenic side-effects (such as adverse effects on the lipid profile, acne, hirsutism, and androgenic weight gain). A low-dose pill has been developed containing the progestogen drospirenone, which has mineralocorticoid activities.[31]

COCs are typically taken in a regimen of 21 "active" hormone pills followed by a hormone-free interval of seven days, during which withdrawal bleeding occurs. The monophasic agents consist of fixed amounts of the estrogen/progestin ingredients in all 21 active tablets. The biphasic and triphasic formulations have 2 or 3 different tablets, respectively, containing varying amounts of hormones, which more closely approximates the usual levels experienced during a woman's menstrual cycle.

Lengthening the hormone-free interval by missing pills at the beginning or end of a cycle may increase the risk of pregnancy by allowing follicular development and ovulation in some patients.[32]

The disadvantages of COCs use for adolescents include the need to take the pill every day (preferably at the same time each day), and the lack of protection against STDs.[32]

Adolescents may choose to start hormonal contraception on the first day of the next menstrual cycle or do a "Sunday start". Starting on the first day of the menstrual cycle allows an adolescent to be reasonably sure that they are not pregnant. Initiating on a Sunday allows for a withdrawal bleed to occur on a Monday, assuming a seven-day hormone-free interval.[28,29,32]

Adolescents often have an irregular lifestyle, difficulties in assessing risk of unintended pregnancy and consequently run a high risk of contraceptive failure and unintended pregnancies. Winner et al.[33] showed that among users of pills, patches, or rings, those who were less than 21 years of age had a risk of unintended pregnancy that was almost twice as high as the risk among older women. In the event of missing a pill, only 25% would use additional contraceptive measures such as condoms.[34]

Other widely used SARC methods are the vaginal ring (delivers 15 µg of EE and 120 µg of etonogestrel

daily) and the patch (delivers 20 µg of EE and 150 µg of norelgestromin daily). Medical eligibility and side effect profiles of both compounds are considered to be the same as for the COCs.[28]

The vaginal ring is a flexible silicone ring measuring 5,4 cm at the outer diameter with 4 mm thickness. The ring is inserted in the vagina and left in place for 3 weeks to release on average 0.120 mg/d of etonogestrel and 0.015 mg/d of ethinyl estradiol hormones daily for birth control. After 3 weeks, it is removed for 1 ring-free week.[28] Patients should be counselled that if the ring is occasionally removed, it must be replaced within 3 hours to maintain optimal efficacy.

The patch is worn for three consecutive weeks (each patch for 7 days), followed by a patch-free week to allow for withdrawal bleeding. The thin plastic patch is worn on the skin (upper extremities, back, lower abdomen, or buttocks but not on the breasts) where it provides a constant flow of these hormones into the bloodstream.[28] According to data from the manufacturer, there is an increase of 60% in the area under the curve for EE compared to a 35 µg COC preparation.

COCs use is associated with a 3.0 to 3.5-fold increase in the relative risk of VTE.[32] However, if there are no additional risk factors, the absolute risk of VTE associated with 20 µg of EE dose is lower, particularly when compared to the risk during pregnancy and post-partum.[32] The risk of VTE is highest in the first few months after initiating COC and lessens over the first year of use.[32]

The safety of different progestogens is conflicting; however, there is evidence that COCs containing levonorgestrel or norethisterone may be associated with lower rates of VTE, stroke, and myocardial infarction than COCs containing the newer generation progestogens.[32]

If the patient has additional risk factors for VTE, the absolute risk is higher, and COCs should not be used. The conditions in which COCs should not be used or are not usually recommended are the same for adolescents and adults.

Estrogen-containing COCs are contraindicated for those with a history of thromboembolism or thrombophilia due to factor V Leiden mutation or to protein C, protein S, or antithrombin III deficiencies; pulmonary artery hypertension; systemic lupus erythematosus associated with antiphospholipid antibody syndrome or renal disease (particularly that associated with hypertension) or severe hepatic dysfunction.[32]

Breast tension, headache and nausea in particular. are much less frequent in women taking very low-dose formulations. Weight gain may be a significant discomfort associated with COCs although a Cochrane analysis did not reveal convincing evidence that use of COCs affects body weight or composition, and if any effect exists, it is likely mild.[35]

For combined hormonal contraceptives (COCs, patches, vaginal rings) interactions with drugs, we suggest consulting an up-to-date medicine formulary.

2. Progestogen-only pills. Progestogen-only pills formulations (POPs) are a suitable alternative for those who wish to use an oral contraceptive but have contraindications to oestrogen use or prefer not to use COCs. POPs thicken cervical mucosa to inhibit sperm penetration and may also prevent ovulation (50% of cycles).[36]

POPS are oestrogen-free oral contraceptives containing 0.35 mg of norethindrone and are taken daily with no hormone-free days. There are no inactive pills in the POP pack and no break required between packs. POPs can be initiated on any day of the menstrual cycle; however, if starting six or more days after the onset of menses, condoms should be used for the first two days (48 hours) of hormone pills.[36]

Norethisterone and levonorgestrel-only pills must be taken within three hours of the regular dosing time each day. Desogestrel-only pills have a wider window for error and must be taken within 12 hours of the regular dosing time.[36]

Most women achieve decreased menstrual bleeding, and 10% achieve complete amenorrhea. Breakthrough bleeding is the most common side effect. POPs should be used with caution in those with some liver diseases, e.g. decompensated cirrhosis or positive for antiphospholipid antibodies.[37]

b. Long-Acting Reversible Contraception (LARC). LARC are defined as methods that require administration less than once per cycle or month. The methods listed below fall within this definition:

Progestogen-only injectable:

- Progestogen-only injectables (Medroxy-progesterone acetate: DMPA, given intramuscularly or subcutaneously)
- Progestogen subdermal implants

Intrauterine contraception:

- Copper intrauterine device (IUCD)
- Levonorgestrel releasing intrauterine system (LNG-IUS)

Subdermal progestogen implants

1. Depot medroxyprogesterone acetate (DMPA). The primary effect of DMPA is to reduce the chance of ovulation by limiting follicle-stimulating hormone and luteinizing hormone secretion.[32] Besides, DMPA injections can alter cervical mucosa to prevent sperm penetration, as well as thin the endometrial lining to make it unsuitable for implantation.[32]

DMPA injections are administered at 12-week intervals (11–13 weeks) for optimal effect. It may be given in a single dose of 150 mg intramuscularly. Lower dose injections of DMPA containing 30% less hormone, given by subcutaneous injections every 13 weeks, are available in some countries. The upper outer quadrant of the buttock (i.e. dorsogluteal site) is the preferred IM injection site; the first injection should be given within the first five days of starting of a menstrual cycle.

This method is convenient for women who do not want to remember to take the pill daily, cannot use the patch, or a contraceptive method at the time of intercourse.[38] Other advantages include lack of estrogen-related adverse effects.

There are 2 specific areas of concern for the use of DMPA in teenagers:

(a) Weight gain: In some patients, DMPA causes increased appetite and weight gain.[39,40] Diet and exercise should be a point of counselling at all visits for patients who are overweight or obese.

(b) Bone health: Another notable side effect is the potential decrease of bone mineral density (BMD), particularly after prolonged use. This is of significant concern in teenagers because girls accrue approximately 30% to 40% of their bone mass during adolescence. The BMD loss appears to be reversible after stopping the DMPA.[41] Adolescent DMPA-users should be counselled for adequate calcium and vitamin D intake, weight-bearing activity, and avoidance of alcohol, caffeine, and smoking which can also contribute to BMD loss.[42]

2. Progestogen-containing contraceptive implant. Long-acting progestogen subdermal implants have been proven to be highly effective and safe. The currently available etonogestrel-releasing subdermal implant is a single rod that measures 4 cm in length and 2 mm in diameter and is composed of an inner ethylene vinyl acetate core embedded with crystals of the progestin active ingredient, etonogestrel.[43]

The single-rod implant consists of a small plastic rod, about the size of a matchstick, placed just under the skin of the upper arm that releases small amounts of progestogen into the body. Implants contain no oestrogen and so are therefore suitable for most women (including breastfeeding) or cannot, or do not wish to use oestrogen. The implants prevent pregnancy by inhibiting ovulation, as well as preventing sperm penetration by altering cervical mucosa.[43] They are the most effective form of reversible contraception and can protect for a period of up to five years. Unlike estrogen-containing contraceptive methods, use of the implant can safely be encouraged in patients with a history of thromboembolic disease, hypertension, those who are overweight or obese, smoke, or are aged 35 and older.[44]

Insertion and removal complications are rare, reported in 0.3% to 1% of insertions and 0.2% to 1.7% of removals. They include local irritation, allergic reaction, infection, and hematoma.[45]

Irregular bleeding is the most common side effect, especially in the first 6 to 12 months. For most women, periods become shorter and lighter, but some will have longer, heavier periods with increased spotting.[46] Skin irritation may occur at the site of placement of the contraceptive rod.

3. Intrauterine contraceptive device (IUD). There are currently two types of intrauterine devices (IUD): levonorgestrel-releasing intrauterine system (LNG-IUD) and copper (Cu) IUD. An IUD provides contraception by preventing fertilisation and preventing implantation of the fertilised egg(s). When used appropriately, IUDs are a generally safe and effective method of contraception with a failure rate of less than 1%.[47,48]

The LNG-IUD consists of a T-shaped polyethylene frame (T-body) with a steroid reservoir around the vertical stem. The reservoir consists of a white cylinder, made of a mixture of levonorgestrel and silicon.[47] The LNG-IUS's (LNG-IUS 20, LNG-IUS 12, LNG-IUS 8) contain different amounts of levonorgestrel in their reservoir.

After insertion of an LNG-IUD, unpredictable bleeding may occur for the first 3–6 months; however, most women will see overall reduced menstrual bleeding thereafter.

The Cu-IUDs may either have a frame (usually T-shaped) or be frameless and contain a varying amount of copper. The Cu-IUD is associated with increased duration and volume of menstrual bleeding.[48]

The success rate for insertion in adolescents is 96%. Before providing or placing an IUD, absolute and relative contraindications should be reviewed, and the procedure should be carefully explained, including the possibility of discomfort or pain during the gynaecological examination and device insertion. The most common side effects are bleeding pattern alterations, vulvovaginitis, abdominal/ pelvic pain, acne, ovarian cysts, and headache.[49-51]

Available options for hormonal contraception in adolescent and young women, including limitations and side-effects are summarized in **table 1**. All contraceptive methods require reliable information on correct use, together with detailed information on how to avoid sexually transmitted diseases (STDs). Additional use of condoms is advised for dual protection.

C. Overview of Contraceptive Practices Followed by Women with SCD and Treatment Safety. Available data on contraceptive methods chosen by women with SCD and on the safety of treatment are limited.

Table 1. Summary of available options for hormonal contraception in adolescent and young adult women.

Therapeutic strategy	Effectiveness and advantages	Limitations	Disadvantages
Combined oral contraceptives	Correct and consistent use effectiveness is as high as 99.7%.	No use by patients with thrombosis, thrombophilia, migraine with aura.	Nausea, inter-menstrual spotting/bleeding, mild headache, breast tenderness, and mood changes. COCs containing drospirenone may cause elevations in potassium among individuals who take potassium-sparing medications.
Transdermal contraception	Effective in pregnancy prevention and compliance.	The same as COCs. Higher failure in women weighing over 90 kg : patch is not recommended.	Disadvantages: lack of privacy when the patch is worn on a visible area, possible skin irritation and pigment change at application site.
Vaginal ring	Discrete; requires removal and insertion only once per month	The same as COCs.	The same as COCs. Vaginitis, leucorrhea, discomfort.
Progestin-only pills (mini-pills)	Safe for women with estrogen contraindications.	Strict adherence in timing of daily dose, difficult for adolescent schedules.	Changes in menstrual bleeding (irregular bleeding, spotting or amenorrhoea). Mild headaches and oiliness of the skin/acne nausea, mood changes and breast tenderness.
Depot medroxyprogesterone acetate	Safe for women with contraindications to estrogen.	Intramuscular injection; reinjection timely.	Irregular, unpredictable, prolonged or heavy bleeding or spotting. Appetite changes/ weight gain. Headache. Decreased bone density with long-term use
Progestin-only implantable	Long duration of action, highly effective contraceptive. May be offered if contraindication to estrogen.	Requires minor procedure for insertion; higher upfront costs. Insertion/removal problems.	Changes in menstrual bleeding, including lighter bleeding, irregular bleeding, infrequent bleeding and amenorrhoea. Acne.
Levonorgestrel-containing intrauterine system (LNG-IUS)	Safe for most women regardless of age.	An IUCD should not be used if the patient has a current STD, pelvic inflammatory disease, or unexplained vaginal bleeding. Discomfort with placement.	Irregular bleeding. Dysmenorrhea. Migration, uterine perforation (rare), expulsion.

In 1984, Samuels-Reid,[52] interviewed 52 patients with HbSS, HbSC, HbS/ß-thal and sickle cell trait. 33% of the study group used a contraceptive method compared with 66% of healthy controls. The most common method in both groups was the birth control pill (39% in the sickle cell group and 86% in the control group). The sickle cell group used a greater variety of contraceptive methods, with the cumulative majority choosing the diaphragm (23%), intrauterine device (15.4%), and foam (23%).

Howard et al.[53] investigated the use of contraceptives and complications in 102 women with HbSS disease, 42 with HbSC, and 12 with HbS/ß-thal. COCs were taken by 67 women (45%); 30 used POPs (20%), 28 intrauterine contraceptive device (19%), and 36 injectable DMPA (17%). These findings were similar to those from North America, where 39% used COCS and 15.4% the intrauterine device.[54]

In this cohort of 156 women using the combined contraceptive pill, four complained of increased frequency of crises (3 of 102 with HbSS disease and 1of 12 HbS/ß-thal), while two reported deep vein thrombosis. The type of pill was not stated, but both were assumed to be low dose preparations because of the prescribing policy of the clinic concerned. Both had HbSS disease.[53]

The fact that over 50% of SCD pregnancies were still unplanned in a 2010 survey confirms that there is a continuing unmet need for effective contraceptive advice for this group of patients, suggesting that further intensive efforts on this issue are needed to educate health care professionals, as well as initiatives to include contraceptive advice in the routine medical care of young women with SCD.[55]

Legardy and Curtis[56] searched the MEDLINE database for articles published between 1966 and September 2004 on the use of progestogen-only contraceptives in women with SCD. Of the 70 articles identified, 8 met the criteria for this review. These studies did not identify any adverse event, or clinically or statistically significant adverse changes in haematological or biochemical parameters associated with the use of progestogen-only contraceptive methods. Six studies suggested that users experienced a decrease in clinical symptoms and less frequent and severe painful crises compared with nonusers.

A Cochrane review by Manchikanti et al.[57] reported similar results. DMPA use in women with HbSS was a safe contraceptive option. In addition, DMPA reduced painful sickle episodes (OR 0.23; 95% CI 0.05 to 1.02). No trial involving estrogen products was reported.

A systematic review that examined the safety of hormonal and intrauterine contraceptive use among

Table 2. Clinical, metabolic and coagulation changes associated with contraception in adolescent and young adult women with sickle cell disease. Review of the literature from 2014 to 2020.

Authors	Patients	Results and Conclusions
Qureshi AI et al. *Thromb Res*. 2015;136:315–318.	178 of 1,257 women (14.2%) with SCD used oral contraceptives.	The four fold higher risk of incidence of stroke associated with use of oral contraceptives in women with SCD can be mitigated by controlling other cardiovascular risk factors.
Whaley NS et al. *Blood.*2015;126: 3263.	54 women with SCD median age 35years completed a self-administered electronic survey.	55% had unintended pregnancy; one third did not use a birth control method at last intercourse. Most common contraceptive methods: surgical sterilization (30%) , condoms (30%) and DMPA (9%). Women were more likely to use estrogen-containing methods (6%) than highly effective long-acting methods like intrauterine devices or contraceptive implants (3%).
Carvalho NS et al. *J Obstet Gynaecol*. 2017; 37:74–77.	54 sexually active women with SCD with. mean age 32 ±11.2 years. 50% had kidney disease and 17% had thrombosis.	Over 80% had used some form of contraception mostly combined hormonal contraceptive (52%) or progestin-only contraceptives (46%). No association was found between the use of combined oral contraceptive pill and major complications.
Day ME et al. *South Med J*. 2019; 112:174–179.	A paper survey at two academic medical centers in 103 SCD women aged 10 to 55 years.	Of 103 women, 53 (51.5%) used contraception, with DMPA injections and condoms being the most common.

women with SCD was performed in 2012. Eight articles met the inclusion criteria. The evidence was of fair to poor quality and suggested that progestin-only and combined hormonal contraception did not affect the frequency of sickle crises or other adverse events and no effect on hematologic parameters associated with sickle crises.[58] No studies examined the risk of thromboembolism in combined hormonal contraceptive users with SCD. There was insufficient evidence to comment on the safety of intrauterine devices.

We searched PubMed for all articles published thereafter, between 2014 and March 2020. Four studies were identified that met the inclusion criteria "contraceptive methods, combined oral contraceptives, short- and long-acting reversible contraception, safety and effectiveness of contraceptive methods, oral contraceptive use and incident stroke, sickle cell disease". The main reported findings are summarized in **table 2**.

D. Medical Eligibility Contraception (MEC) Recommendations. Recommendations for the safety of contraception in women with certain characteristics or medical conditions are provided in the form of MEC from WHO, CDC, Faculty of Sexual and Reproductive Healthcare, and other international organizations.[59-61] WHO and CDC also developed Selective Practice Recommendations for Contraceptive Use recommending which tests and examinations should be performed before providing contraception.[62,63]

The international recommendations are intended to assist health care providers in counselling women, men, and couples about the choice of contraceptive method. For each medical condition/characteristic, contraceptive methods are classified in one of four categories to determine contraceptive eligibility:

- **Category 1 =** Conditions for which there are no restrictions for the use of the contraceptive method.
- **Category 2 =** Conditions for which the advantages of using the method generally outweigh the theoretical or proven risks.
- **Category 3 =** Conditions for which theoretical or observed risks usually outweigh the advantages of using the method. The implementation of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider since the method is not usually recommended unless other more appropriate methods are not available or not acceptable.
- **Category 4 =** Conditions that represent an unacceptable health risk if the contraceptive method is used.

SCD is considered a “prothrombotic” state because of abnormal RBC rheology, hyperviscosity, endothelial dysfunction, and red cells adhesion;[64,65] increased platelet activation; venous sludging and abnormal coagulation associated with increased thrombotic complications in patients receiving estrogens.[66]

Moreover, VTE, defined as deep vein thrombosis (DVT) or pulmonary embolism (PE), is a frequent and severe clinical complication in adults with SCD, and is likely, at least in part, to be the result of this hypercoagulable state. Up to 12% of patients with SCD have a VTE by 40 years of age.[67]

Therefore, the use of certain contraceptives may exacerbate medical disorder and the risk of complications.

In women with SCD, COCs are classified as level 2, meaning that “the advantages of using the method generally outweigh the theoretical or proven risks.” The benefits of estrogen-containing methods usually outweigh the risks of unintended pregnancy. The progestin-only pill, injection, implant and IUD all received a “1” rating (substantially can be used without restriction) from the CDC.[60]

There are few contraindications to progestin-only methods: current breast cancer (Category 4), breast

cancer remission within five years, severe cirrhosis, hepatocellular adenoma, malignant liver tumour, and unexplained vaginal bleeding (Category 3),[60] use of medications to treat seizures or tuberculosis (i.e., phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine, or rifampicin),[72] and evidence suggesting an increased risk of VTE with the use of injectable DMPA.[73]

The copper IUD has a "2" classification rating due to the possibility of heavier menses with this method.[59,60]

These recommendations are meant to serve as a source of clinical guidance; however, individual patient's decision needs to be considered in special risk situations for SCD patients. Such decisions often require interdisciplinary consultation, particularly when the patient suffers from a specific medical condition that is outside the gynaecological sphere, such as: previous stroke, pulmonary hypertension, renal impairment, autosplenectomy, and hepatobiliary complications.

At present, more than 50% of SCD patients survive beyond the fifth decade. This improvement in survival in developed countries has resulted from the close clinical and laboratory follow-up and symptomatic treatment.[74] As patients with SCD get older, there are general or specific risks for developing co-morbidities that were not or rarely seen in the younger SCD population, e.g. silent infarcts, which do not manifest overtly but can accumulate over time, renal failure, and iron overload (especially on frequent transfusions).[75]

Sickle cell hepatopathy is a spectrum of disease manifestations with varying levels of severity due to acute or chronic changes of the hepatobiliary system.[76,77]

In addition to the risk of VTE associated with low-dose COCs use, estrogens and progestogens are cleared through hepatic metabolism, and estrogens act directly on the liver independently of administration route.[78] Long-term use of COCs may be related to the development of hepatocellular carcinomas and adenomas.[79] Finally, estrogens can alter the biliary function and increase cholesterol saturation, which requires special caution (Category 3) when COCs are used in patients with gall bladder disease.[59-61] Hormonal contraceptive use has also been incriminated as a risk of hepatobiliary damage.[80]

Overall, before selecting the appropriate contraceptive method for a woman with SCD, the prescriber should carefully evaluate her medical history and current disease status. The prescriber has to consider not only the WHO-MEC, which are evolving, but also the international guidelines and specialised books[81] to determine the possible contraindications to the contraceptive methods desired by the woman or couple, and decide the most appropriate, and avoiding risk factors especially: obesity, smoking, immobilization, lower extremity injury and surgery wherever possible (**tables 3-6**).[82]

E. Reproductive Medical Counselling. Over the past 20 years, we have steadily progressed in the management of patients with SCD. Long-term therapies, with chronic transfusions, hydroxyurea (HU), and hematopoietic stem cell transplantation (HSCT) have reduced SCD-related morbidity and mortality. Thus, many more children and adolescents with SCD grow into adulthood and face serious considerations regarding childbearing, which is one of the most important factors for quality of life.

There has been very little research on reproductive attitudes, beliefs and health knowledge of patients with SCD.[83-87] The decision to have a child is influenced by the risks of the genetic transmission, the perceptions

Table 3. General risk conditions that may have an impact on eligibility criteria for contraceptive use (From ref. 60 - modified).

Condition	Sub-Condition	Cu-IUD	LNG-IUD	Implant	DMPA	POP	COC
Age		Menarche to <20 yrs:2 ≥20 yrs:1	Menarche to <20 yrs:2 ≥20 yrs:1	Menarche to <18 yrs:1 18-45 yrs:1 >45 yrs:1	Menarche to <18 yrs:2 18-45 yrs:1 >45 yrs:2	Menarche to <18 yrs:1 18-45 yrs:1 >45 yrs:1	Menarche to <40 yrs:1 ≥40 yrs:2
Obesity	a) Body mass index (BMI) ≥30 kg/m²	1	1	1	1	1	2
	b) Menarche to <18 years and BMI ≥ 30 kg/m²	1	1	1	2	1	2
Smoking	a) Age <35	1	1	1	1	1	2
	b) Age ≥35, <15 cigarettes/day	1	1	1	1	1	3
	c) Age ≥35, ≥15 cigarettes/day	1	1	1	1	1	4
Dysmenorrhea	Severe	2	1	1	1	1	1

Table 4. Medical eligibility for initiating and continuing combined hormonal contraception: Absolute and relative contraindications (From ref. 59 - modified).

CONDITION	CATEGORY			
	COC	P	CVR	CIC
	COC = combined oral contraceptive P = combined contraceptive patch CVR = combined contraceptive vaginal ring CIC = combined injectable contraceptive			
DEEP VEIN THROMBOSIS (DVT)/ PULMONARY EMBOLISM (PE)*				
a) History of DVT/PE	4	4	4	4
b) Acute DVT/PE	4	4	4	4
c) DVT/PE and established on anticoagulant therapy	4	4	4	4
d) Family history (first-degree relatives)	2	2	2	2
e) Major surgery				
i) with prolonged immobilization	4	4	4	4
ii) without prolonged immobilization	2	2	2	2
f) Minor surgery without immobilization	1	1	1	1

Table 5. Medical eligibility for initiating and continuing progestogen-only contraception: Absolute and relative contraindications (From ref. 59 - modified).

CONDITION	CATEGORY		
	POP	DMPA/ NET-EN	LNG/ETG
DEEP VEIN THROMBOSIS (DVT)/ PULMONARY EMBOLISM (PE)*			
a) History of DVT/PE	2	2	2
b) Acute DVT/PE	3	3	3
c) DVT/PE and established on anticoagulant therapy	2	2	2
d) Family history (first-degree relatives)	1	1	1
e) Major surgery			
i) with prolonged immobilization	2	2	2
ii) without prolonged immobilization	1	1	1
f) Minor surgery without immobilization	1	1	1

POP = progestogen-only pill
LNG/ETG = levonorgestrel and etonogestrel (implants)
DMPA = depot medroxyprogesterone acetate (injectable)
NET-EN = norethisterone enanthate (injectable)

of the disease severity and the risks of pregnancy to the mother and fetus. All are essential components in the clinical management of SCA patients with significant medical, psychological, social, ethical and legal implications.

Accordingly, it is of utmost importance that health

Table 6. Medical eligibility for initiating and continuing intrauterine device contraception: Absolute and relative contraindications (From ref. 59 - modified).

CONDITION	CATEGORY	
	Cu-IUD	LNG-IUD
DEEP VEIN THROMBOSIS (DVT)/ PULMONARY EMBOLISM (PE)*		
a) History of DVT/PE	1	2
b) Acute DVT/PE	1	3
c) DVT/PE and established on anticoagulant therapy	1	2
d) Family history (first-degree relatives)	1	1
e) Major surgery		
i) with prolonged immobilization	1	2

providers have a fundamental understanding of the disease and be aware of relevant professional management guidelines to encourage knowledgeable reproductive health decisions.

Although there is a paucity of information on provider knowledge and practice related to hemoglobinopathies internationally, the Royal College of Obstetricians and Gynaecologists[88] has established guidelines for the management of hemoglobinopathies in pregnancy and released recent recommendations for the management of SCD in pregnancy based on the available evidence.

Conclusions and Recommendations. Patients with SCD seen in haematology practice are incredibly heterogeneous in clinical and haematological phenotypes with multiple clinical issues that must be faced. Acute and chronic vessel(s) occlusion causes significant complications in various organs, including brain, kidneys, bones, lungs, liver, spleen, and gastrointestinal tract.

Furthermore, women with SCD are known to have high-risk pregnancies, mainly affecting the foetus. The mothers also face serious maternal risks, such as an increased risk of both medical complications (infections and thromboembolic events) and pregnancy-related complications (preeclampsia, eclampsia, preterm labour, placental abruption, and fetal growth retardation).[19] The maternal and fetal mortality rates during pregnancy can attain 11.4% and 20%, respectively.[20,89]

Women with SCD also have higher rates of Caesarean deliveries.[90]

The cornerstones of treatment for SCD patients involve the management of painful vaso-occlusive, hemolytic and aplastic rises, hemolytic anaemia, other disease complications, and prevention of infection.

Blood transfusions (especially exchange transfusions), the first disease-modifying therapy used for SCD, reduces the percentage of circulating RBCs with HbS. However, the need for repeated venous access and the associated risks and complications, such as alloimmunization and iron overload, limits its use.[85,86,91,92] Chelation therapy can be used to remove excess iron in patients with evidence of iron overload.[91] During pregnancy, chelation should be restricted for cases where the potential benefit outweighs the potential fetal risk.

HU improves several clinical outcomes, such as decrease of vaso-occlusive crisis (VOC) and acute chest syndrome (ACS), reduction of mortality, and decrease for RBC transfusions and hospitalizations. HU works primarily by increasing the level of fetal haemoglobin (HbF), which prevents sickling.[92-95] At present, it is recommended that HU should be discontinued at least 3 months before conception[96] due to the risk of teratogenic side effects.[97-99]

Women with SCD have little knowledge about the risks associated with contraceptive use,[100] and thus, they need guidance for adequate reproductive family planning and unintended pregnancy.

Women with SCD primarily received contraceptive counselling from gynaecologist providers, and only 30% reported a different source.[100]

Contraception should be discussed during transitional care and at regular review; the woman should be fully informed on the advantages and disadvantages of the available methods. The full range of choices should be offered to women with SCD, though some methods may be more suitable.

When assessing the safety of contraceptive methods in women with SCD, any co-existing medical conditions that contraindicate the use of a specific method must be considered carefully.

Women should be informed that in the general population, the risk of venous thromboembolism with the use of COCs is approximately doubled compared to non-users. For SCD patients, there is a lack of evidence on whether this risk is further increased and whether the risk of VTE is reduced in subjects taking COC with a low dose of EE.

The World Health Organization recommends that all contraceptive methods may be prescribed for women with SCD, but the progestogen-only contraceptive methods are preferred (due to no reported increased incidence of venous or arterial thrombosis). The benefits of estrogen-containing methods usually outweigh the risks of unintended pregnancy (Level 2).

However, there is reluctance on the part of physicians to prescribe hormonal contraception in women with SCD based on the assumption that additional risks may be compounded to the underlying disease process; they are often instinctively reluctant to propose the use of the intrauterine contraceptive device because of the potential complications of menorrhagia, exacerbating the chronic anaemia of SCD. That may provoke potentially sickling episodes and infections.

Appropriate treatment requires the active involvement of health care professionals with experience in the management and treatment of SCD, usually a haematologist working in conjunction with a multidisciplinary team, although subspecialists may also have limited experience in the care of SCD-related complications.

Therefore, there is a real need for an integrated approach for selecting suitable contraception for women with SCD by a team of haematologists, gynaecologists, endocrinologists, and primary care providers to support sound communication strategies and collaborative efforts, and share responsibility, mutual understanding and acceptance of each provider's role, within the practice. We hope that this synergy can play a significant role in identifying the safest contraceptive method that preserves patient health status and abolish the risks of unintended pregnancy.

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