ELSEVIER

Contraception 73 (2006) 195–204

Contraception

Review article

Progestogen-only contraceptive use among women with sickle cell anemia: a systematic review

Jennifer K. Legardy*, Kathryn M. Curtis

WHO Collaborating Center in Reproductive Health, Division of Reproductive Health, Centers for Disease Control and Prevention, Atlanta, GA 30341, USA

Received 27 July 2005; accepted 11 August 2005

Abstract

The use of progestogen-only contraceptives among women with sickle cell anemia has generated concerns about possible hematological and other clinical complications. Based on the literature, we assessed whether use of progestogen-only contraceptives is associated with adverse health effects among women with sickle cell anemia. We searched the MEDLINE database for articles published in peer-reviewed journals between 1966 and September 2004 that were relevant to sickle cell anemia and use of progestogen-only contraceptives. Of the 70 articles identified through the search, 8 met the criteria for this review. These studies did not identify any adverse events or clinically or statistically significant adverse changes in hematological 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. Although data are limited, these studies suggest that progestogen-only contraceptives are safe for women with sickle cell anemia.

Keywords: Sickle cell anemia; Progestogen; Contraception; Systematic review

1. Introduction

Sickle cell disease is caused by the pairing of an inherited autosomal recessive gene (β-globin), which affects the red blood cells [1,2]. Deoxygenation of the red blood cells causes these cells to change from their normal round shape to a rodlike sickle shape. These sickle-shape cells adhere to the blood vessels, eventually clogging the vessels and blocking normal flow of blood and oxygen to organs and tissue. Of the several forms of this disease, the most common and severe is sickle cell anemia. Primarily, people of African and Mediterranean ancestry are affected by the disease and often are carriers of the trait. Based on statistics from the National Heart, Lung, and Blood Institute, in the United States, approximately 1 in every 500 African American babies and 1000–1400 Hispanic American babies are diagnosed with this disease each year. The sickle cell trait (one copy of the gene that causes sickle cell anemia) is present in an estimated 2 million Americans [3]. The medical complications that arise from this disease include chronic anemia, episodes of musculoskeletal pain or "crises," acute chest syndrome and stroke. In addition, sickle cell disease in women has been associated with significant maternal morbidity and mortality [4,5].

Using contraception and becoming pregnant are major decisions for a woman with sickle cell anemia because of the related medical complications. Historically, it has been recommended that women with sickle cell anemia avoid pregnancy, become sterile or have an abortion because of the increased risk of maternal and fetal mortality [4,5]. Maternal and perinatal mortality rates associated with sickle cell disease have declined significantly over time, due to advancements in medical technology and obstetric and perinatal care. However, a recent study showed that women with sickle cell anemia still have an increased risk of pregnancy complications, such as premature rupture of the membranes, preterm labor, antepartum admission and postpartum infections [5].

Women with sickle cell anemia who want to avoid pregnancy need to have appropriate and reliable counseling regarding contraceptive use. However, there have not been any clear universal guidelines established for contraceptive

* Corresponding author. Tel.: +1 770 488 6513; fax: +1 770 488 6391.

E-mail address: jlegardy@cdc.gov (J.K. Legardy).

0010-7824/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.contraception.2005.08.010

use among these women. Traditionally, sickle cell disease has been considered a contraindication to the use of combined oral contraceptives (COCs), especially in Europe [6]. Yet, evidence is limited regarding the effects of COC use in this population [2,6–8]. The World Health Organization (WHO) currently classifies sickle cell anemia as a Category 2 for COCs, meaning that the benefits of COC use among women with this condition generally outweigh the theoretical or proven risks [9]. There have also been concerns about the safety of using intrauterine devices (IUDs) for women with sickle cell disease, but studies have shown that copper IUDs are a safe method of contraception for these women [6,10]. In addition, WHO classifies sickle cell anemia as Category 1 for IUD use, meaning there is no restriction for their use [9]. For progestogen-only contraceptives (i.e., pills, injectables and implantables), possible hematological and other clinical complications are the major concerns regarding the use of these contraceptives among women with sickle cell anemia.

We conducted this systematic review in preparation for an Expert Working Group of international family planning experts convened by WHO in October 2003 to develop and revise medical eligibility criteria for contraceptive use. In this report, we evaluate the scientific evidence regarding whether women with sickle cell anemia experience adverse health effects while using progestogen-only contraceptives, as well as provide the WHO recommendations that were derived in part from this evidence. We considered the following progestogen-only contraceptive methods: Norplant and Norplant-2 or Jadelle (levonorgestrel-releasing contraceptive implants), Implanon (etonogestrel-releasing contraceptive implants), Uniplant (nomegestrol acetate-releasing contraceptive implants), depot medroxyprogesterone acetate (DMPA) injectables, norethisterone enanthate (NET-EN) injectables and progestogen-only contraceptive pills (any formulation).

2. Materials and methods

We searched the MEDLINE database for articles (in all languages) published in peer-reviewed journals from 1966 to September 2004. Search terms included “sickle cell disease” or “anemia” along with the following terms: (a) depot and medroxyprogesterone 17-acetate or medroxyprogesterone acetate, (b) DMPA, (c) progestogen-only contraception or progestational hormones or progestogen and only and contraceptive agents, (d) norethisterone-enanthate, (e) NET EN, (f) contraception, (g) contraception or female contraception, (h) implants, (i) Norplant, (j) Uniplant, (k) Jadelle, (l) Implanon, (m) levonorgestrel, (n) etonogestrel, and (o) effects and contraceptive agents or contraceptives.

We also searched the reference lists of the articles identified by the electronic search and letters to the editor to identify additional relevant articles. We did not consider unpublished manuscripts, dissertations or abstracts from scientific conferences.

2.1. Study selection

Seventy articles were identified by searching MEDLINE and by reviewing reference lists. Eight of the 70 articles matched the goal of the review, which was to evaluate health outcomes related to progestogen-only contraceptive use among women with sickle cell anemia. These articles were selected after reviewing the titles, abstracts and articles. The eight articles examined the safety of using different progestogen-only contraceptive methods among women with sickle cell anemia, including clinical and other hematological effects.

2.2. Study quality assessment

We summarized and systematically assessed the evidence using a standard abstract form. Each article was reviewed for quality using a preliminary draft of the grading system developed by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group (Appendix A) [11].

2.3. Data synthesis

This review includes two randomized controlled trials (RCTs), two non-randomized controlled trials, two prospective cohort studies and two cross-sectional studies (Table 1). Due to the overall low prevalence of sickle cell anemia in the general population, the sample sizes of these studies were small. The studies reported means and standard deviations, percentages or qualitative results, so summary odd ratios were not calculated.

3. Results

3.1. Implantables (Norplant, Norplant-2, Jadelle and Uniplant)

A prospective cohort study conducted in Nigeria evaluated the safety of Norplant use among 25 women with homozygous sickle cell anemia [12]. These women were followed for a mean of 12 months after insertion. Outcomes were measured pre- and postinsertion for each woman, and the women served as their own controls. At baseline, these women had not experienced a painful crisis or serious infection in the past month; had no clinical evidence of gall bladder disease; and had no history or evidence of aplastic crisis, diabetes, bleeding disorders, myocardial infarction, stroke or severe liver, renal, skeletal, pulmonary, skin or ocular disease. Insertion of the Norplant did not cause any serious or unexpected adverse side effects. By using paired t tests, this study showed no statistically significant changes after Norplant was inserted in the means of any of the five biochemical and six hematological parameters measured. For example, the fetal hemoglobin (HbF) percent (hematological parameter) pre- and postinsertion mean was 3.1 and 3.4, respectively. For the serum albumin (biochemical parameter), the pre- and postinsertion mean was 3.8 and 3.9, respectively. This study

had a high retention rate (23/25 participants) that allowed for 80% power to detect an adverse event occurring in 7% of the participants.

In two studies conducted in Brazil, which examined the effects of Uniplant, no adverse effects were reported among women with sickle cell anemia. Ten otherwise healthy women of reproductive age with sickle cell anemia were enrolled in a 1-year, prospective cohort study to examine the effects of using Uniplant on carbohydrate metabolism [13]. These participants had no contraindications to hormonal contraceptives and had not used a hormonal contraceptive in the past 6 months. The outcomes of interest were glucose tolerance and insulin levels, measured pre- and postinsertion, and the women served as their own controls. Participants did not experience any changes in these outcomes during the study period. The women's fasting glycosylated hemoglobin levels before insertion ranged from 77 to 90 mg/dl, and by the end of the study, their levels were 76 to 93 mg/dl. Similarly, the serum insulin levels did not vary significantly pre- and postinsertion. A non-randomized controlled trial assessed the safety and clinical effects of Uniplant use among 30 women with sickle cell anemia (20 Uniplant users and 10 nonusers) [14]. Women who received Uniplant showed a significant decline in the number of clinical symptoms (e.g., headaches, body weakness and limb pain), had no painful crises in the first 6 months of follow-up compared to the control group (50% and 30% at 1 and 3 months, respectively), and after 6-months, both groups experienced infrequent mild crises. After analyzing the hematological and biochemical parameters, only one parameter showed a significant change. In the Uniplant group, the F-cell percentage, which is the proportion of red blood cells with HbF, increased during 1 year of follow-up (6.6% and 14.04% at baseline and 12 months, respectively) compared with the nonuser group (3.6% and 4.1%, respectively).

3.2. Injectables (DMPA and NET-EN)

One non-randomized controlled trial compared the effects of DMPA with a COC (Microgynon) on the frequency and intensity of painful crises in 43 homozygous sickle cell patients [15]. This trial was conducted at the WHO Collaborative Centre for Research contraceptive clinic in Panama. Thirteen women received DMPA, 14 received COCs and 16 were controls. Although authors state that the groups were randomly assigned, the process is unclear because the third group consisted entirely of surgically sterilized patients. There were no significant differences between the three groups in their hematological parameters during follow-up. However, 50% of women in the DMPA group were pain free by 3 months and 70% in this group by 12 months. This experience was similar in the COC group, but at lower rates (27.3% at 3 months and 55.5% at 12 months). For the control group, 8% and 50% were pain free by 3 and 12 months, respectively.

An RCT that included a crossover period assessed the hematological and clinical effects of DMPA use on homozygous sickle cell disease patients in Jamaica [16]. Twenty-five women were enrolled at a hospital for a 2-year period. Women received three injections of either DMPA or saline at 3-month intervals, and then experienced a 6-month washout period. After the washout period, they received three injections, 3 months apart, of the alternate preparation; the order of the administration was randomly chosen. Women experienced rises in their average level of fetal HbF, total hemoglobin, red cell count, red cell mass and red cell survival while using DMPA. During the DMPA phase, the mean and standard deviation for the red cell count at baseline was 0.94 (0.17) and at 30 weeks was 1.03 (0.18) compared to the placebo phase during which no significant change occurred between the time intervals. Results also showed decreases in reticulocytes, irreversibly sickle cell (ISC) counts and total bilirubin levels during the DMPA phase of the study. During the 30-week period, 29 and 59 episodes of bone pain were experienced by 61% of the women in the DMPA phase and 87% of the women in the placebo phase, respectively.

We did not identify any studies evaluating use of NET-EN among women with sickle cell disease.

3.3. All progestogen-only contraceptives

Two cross-sectional studies showed no adverse effects among women with sickle cell disease and use of various types of contraceptives (i.e., COCs, Depo-Provera and IUDs). A study of 30 women with sickle cell disease at two London hospitals examined the effects of estrogen and progestogen contraceptives on the red cell deformability at atmospheric partial oxygen pressure (pO_2) [17]. This cross-sectional study divided women into three categories: women not using exogenous hormones, women using monophasic COC pill (COC) and women using progestogen-only contraceptives. Participants using progestogen-only contraceptives (type not specified) experienced a lower mean clogging rate (2.5 ± 0.7) compared with the COC group (3.0 ± 1.6) and control group (4.3 ± 0.7). The red cell transit time for the progestogen-only group was 23.6 ± 0.7 compared with the control group (26.6 ± 17.9); however, the COC group red cell transit time was lower than progestogen-only group (21.7 ± 6.1).

In the other study, 164 women with sickle cell hemoglobinopathies were included in a cross-sectional study to determine whether they experienced complications while using contraceptives [18]. Among 67 COC users, 5.9% reported an increase in painful crises, compared with 3.6% of the 28 IUD users and none of the 26 DMPA users. (Authors did not report on statistical significance.)

3.4. Oral megestrol acetate

To measure the effects of a progestational agent on sickling in vitro after oral administration, an RCT was conducted with eight Nigerian teenagers (seven females and one male with sickle cell anemia) [19]. The randomization and assigning processes were unclear. However, all participants received 6 weeks of megestrol acetate and then

Table 1
Evidence table for progesterone-only contraceptive use among women with sickle anemia

Author (year)	Objective	Study design	Outcome	Results	Strengths	Weakness	Grading of quality
Ladipo et al. (1993) [12]	Evaluating the safety of Norplant implant in women with sickle cell disease	Prospective cohort study conducted at the University College Hospital in Ibadan, Nigeria; 25 women with homozygous sickle cell disease; 18–40 years of age; no painful crises or serious infection in the past month, no clinical evidence of gall bladder disease,no history or evidence of aplastic crisis, diabetes, severe liver, renal, skeletal, pulmonary, skin, ocular or bleeding disorders, myocardial infarction or stroke. The follow-up period was for 1–29 months after insertion	Assessing changes in hematological parameters (PCV, MCV, reticulocytes, ISCs, HbF and total bilirubin) and biochemical parameters (HDL cholesterol, aspartate transaminase, alkaline phosphate, serum creatinine, serum albumin)	1. The use of Norplant did not cause any serious or unexpected adverse side effects 2. No significant changes (biochemical or hematological) occurred after insertion of the Norplant	1. Retained 23 of 25 participants, which allowed for 80% power to detect an adverse event occurring in 7% of participants	1. No clear statement of hypothesis	Low
Barbosa et al. (2001) [13]	Measuring the changes in carbohydrate metabolism in sickle cell patients who use Uniplant	Prospective cohort study conducted by the maternity hospital of the Federal University of Bahia, Salvador, Bahia, Brazil; 10 healthy sickle cell women of reproductive age; the women had no contraindications to hormonal contraceptives; none had used a hormonal contraceptive 6 months prior to recruitment	Changes were measured in blood glucose, insulin levels, fasting glycosylated	1. No adverse effects or pregnancies during the study period 2. No clinical changes 3. Fasting glycosylated hemoglobin did not significantly change 4. Serum insulin levels before and after insertion of the Uniplant did not vary significantly		1. Small sample size	Intermediate
Nascimento et al. (1998) [14]	Assessing the safety and clinical effects of Uniplant in homozygous sickle cell patients	Non-randomized controlled trial conducted at the Hospital Edgard Santos at Federal University of Bahia, Salvador, Bahia, Brazil; 30 sickle cell anemia women (20 Uniplant and 10 control); 18–40 years old; no history or evidence of aplastic crisis, diabetes, severe liver, renal, skeletal, pulmonary, skin, ocular or bleeding disorders, myocardial infarction or stroke, no clinical evidence of gall bladder disease, and no painful crises or serious	16 hematological and 18 biochemical parameters were assessed; incidence of painful crises and clinical symptoms was measured	1. Uniplant group experienced no painful crises in the first 6-months and last 6 months. Some had occasional but mild crises, which did not require hospitalization	1. There was a high retention rate	1. This was a non-randomized controlled trial	Intermediate

		infection or blood transfusion in the previous 3 months		2. Uniplant group showed a significant decline in the incidence of clinical symptoms (e.g., headache, body weakness and pain) up to the first 9 months, then recurrence occurred with milder severity 3. The use of nomegestrol acetate did not cause any serious or adverse events during 1 year of observation and patients opted to continue with the use 4. Significant variations of the F-cell percentage for the Uniplant group during 1-year of follow-up			
de Abood et al. (1997) [15]	Measuring the effects of Microgynon and Depo-Provera on the intensity and frequency of painful crises in sickle cell patients	Non-randomized controlled trial at the WHO Collaborative Centre for Research contraceptive clinic in Panama; 43 female, homozygous sickle cell patients; aged 17–39; only women with a history of at least one painful crisis per month. Groups: (1) DMPA ($n=13$); (2) Microgynon ($n=14$); (3) Control ($n=16$, surgically sterilized)	Occurrence and intensity of painful crises; hematological patterns (hemoglobin, hematocrit, reticulocyte, prothrombin time and thromboplastin time)	1. No adverse side effects reported 2. Blood parameters did not change at any time during follow-up 3. DMPA (Depo): 50% of women at first follow-up visit were pain free and this increased to 70% by the fourth trimester (statistically significant) 4. The percentage of Microgynon patients who reported not	1. This study was a randomized comparison between progestin-only contraceptive and COC	1. Does not describe the randomization process 2. This was not blinded because of the different types of contraceptives used	Intermediate

(continued on next page)

Table 1 (*continued*)

Author (year)	Objective	Study design	Outcome	Results	Strengths	Weakness	Grading of quality
de Abood et al. (1997) [15]				experiencing painful episodes increased, but at a lower rate than Depo group. 72.7% reported painful episodes in the first trimester and decrease to 45.5% in fourth trimester			
De Ceulaer et al. (1982) [16]	To assess the hematological and clinical effects of Depo-Provera on homozygous sickle disease patients	2-year RCT, which included a crossover period; 25 women aged 20–41 years who were using some form of contraception and had not used Depo; recruited at the University Hospital of the West Indies in Jamaica	Assessed the clinical (bone pain) and hematological effects (HbA, HbF, total Hb, MCHC, red cell count, mean cell volume, reticulocytes, ISC count, total bilirubin, red cell survival, red cell mass and plasma volume)	1. DPMA was well tolerated by all patients and no local side effects 2. Six patients experienced heavier than normal uterine bleeding 3. DMPA phase: 14 patients experienced 29 episodes of bone pain. Placebo phase: 20 patients experienced 58 episodes 4. Placebo phase: hematological baseline values were not significantly changed. DMPA phase: noticeable rises in the average level of HbF, total hemoglobin, red cell count, red cell mass and red cell survival, and decreases in reticulocytes, ISC counts, and total bilirubin	1. The study was randomized crossover study, which included an appropriate washout period 2. The laboratory technicians were blinded to the type of injection being provided 3. The main outcomes were appropriately measured	1. The main hypothesis was not clearly stated	High

Yoong et al. (1999) [17]	Measure the effects of estrogen and progesterone contraceptives on sickle cell deformability at atmospheric pO_2	Cross-sectional study of women with sickle cell anemia ($N=30$) recruited at hematology clinics at two London teaching hospitals; had not had sickling crises, received a blood transfusion or been pregnant in previous 3 month. Groups: (1) Women not on exogenous hormones; (2) Women on COCPs (specifically the monophasic); (3) Women on progestogen-only contraceptives.	Clogging rates and red cell transit time were measured	1. Progestin-only contraceptives: mean clogging rate was lower (2.5 ± 0.7) than in the COCPs and control group (3.0 ± 1.6 and 4.3 ± 0.7) 2. Mean red cell transit time was lower (23.6 ± 0.7) than the control group (26.6 ± 17.9) and a little higher than in the COCP (21.7 ± 6.1) 3. No adverse effects associated with the contraceptive use on the red cell deformability	1. There was a comparison group	1. Cannot assess temporal association 2. All progestin-only contraceptives with varying doses were lumped together 3. Venesection was conducted at different time intervals depending on the type of contraceptive	Low
Howard et al. (1993) [18]	Determine whether women with sickle hemoglobinopathies suffer complications from contraceptive use	Cross-sectional study; women were interviewed at their local hospital or home near London; 164 sickle cell women (42 HbSC, 12 HbSβ thalassanemia, 102 homozygous). Contraceptive groups: (1) Combined oral contraceptive (COC); (2) Progestogen-only pill (POP); (3) Intrauterine contraceptive device (ICD); (4) Injectable progestogen (IP)	The incidence of side effects (e.g., irregular bleeding, dysmenorrhea, menorrhagia, weight gain, nausea, infection, headaches, migraine, deep vein thrombosis, increased crises) that occurred after taking a particular contraceptive	1. POP ($n=30$): six irregular bleeding, two discontinued for side effects 2. IP ($n=26$): eight irregular bleeding, three discontinued; no reports of serious side effects by women 3. COC ($n=67$): three irregular bleeding, four increased crises, discontinued 4. ICD ($n=28$): five infected, 11 menorrhagia, none discontinued	1. Large sample size 2. Examined different types of contraceptives	1. Cannot assess temporal association 2. Crises were not measure for every contraceptive type	Low

(*continued on next page*)

Table 1 (*continued*)

Author (year)	Objective	Study design	Outcome	Results	Strengths	Weakness	Grading of quality
Adadevoh and Isaacs (1973) [19]	Measuring the effects of progestational agent on sickling in vitro after oral administration	RCT with crossover conducted; 6-week period of each placebo group (vitamins) and megestrol acetate; eight teenage Nigerian patients; seven females and one male with sickle cell anemia. None of the sickle patients were in crisis and pain free in the preceding month, had not received a blood transfusion in the preceding year and were not suffering from other disease; recruited at the University College Hospital, Ibadan, sickle anemia clinic	Percent sickling in vitro and the number of patients who improved were measured	1. Overall, sickling occurred higher among megestrol acetate patients at 1-h period 2. Individual sickling rates were the same as the group rates for the megestrol acetate group 3. The irreversible sickled cells in the subjects do not appear to be affected by megestrol acetate	1. RCT	1. Washout period was not described 2. Randomization was not described 3. Small sample size 4. Different doses were administered that were not consistent with typical contraceptive dosage	Very low

PCV, packed cell volume; MCV, mass cell volume; HDL, high-density lipoprotein; HbA, hemoglobin A; Hb, hemoglobin; MCHC, mean corpuscular hemoglobin concentration; ISC, irreversibly sickled cells; HbF, fetal hemoglobin.

placebo or vice versa. Capsules of 500 μg megestrol acetate were administered once a week for 1 week, then twice in the second week and daily in the third week. A multivitamin, which was used as the placebo, was administered on the same schedule. The megestrol acetate did not cause any adverse effects among sickle cell anemia patients, and it did not seem to affect the irreversibly sickled cells. None of the megestrol acetate patients experienced bone pain during the study compared to 50% of the placebo group who experienced mild bone pain.

4. Discussion

Overall, these studies found no clinically or statistically significant adverse effects associated with progestogen-only contraceptive use among women with sickle cell disease. In fact, several studies suggested that progestogen-only contraceptive users had significantly better outcomes when compared to nonusers. The results from a majority of the studies reported that clinical symptoms (e.g., painful crises, headache, body weakness) improved during the time in which the participants were receiving the progestogen-only contraceptive [14–16,18,19]. Improvements in biochemical and hematological parameters (i.e., red cell deformability, HbF, clogging rate and red cell transit time) were also reported.

This systematic review is limited by the number of studies that were available. In addition, the design, methods of analysis and methods for measuring the hematological and clinical complications associated with taking progestogen-only contraceptives varied from study to study. Nevertheless, the overall methodological quality of the studies was considered to be "intermediate." Seven of the eight studies reviewed had small sample sizes, but the retention rate for these studies was relatively high [12–17,19].

Although the studies had limitations, the overall findings are consistent in showing no negative effects associated with using progestogen-only contraceptives among women with sickle cell disease. Some evidence suggested that it may be beneficial (clinically and biochemically) for this population to use progestogen-only contraceptives. Based in part on these findings, the WHO has recommended that sickle cell anemia be classified as a Category 1 for progestogen-only contraceptives, meaning that there are no restrictions for use of these contraceptives among women with sickle cell anemia [9].

Acknowledgments

This review was supported by resources from the World Health Organization, the U.S. Centers for Disease Control and Prevention (CDC), U.S. Agency for International Development (USAID) and the U.S. National Institute of Child Health and Human Development (NICHD).

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the funding agencies.

Appendix A. Study quality assessment

Individual study: Each study was given a rating of very low, low, intermediate or high based on the interval validity of the study. If the study was indirect, the quality of the individual study was lowered by one level. If the study was direct, the quality of evidence was kept the same. Similarly, if there was sparseness of the data, the quality of the individual study was lowered by one level.

Body of evidence: The quality of the body of evidence was the highest rating given to an individual study. If the results were inconsistent, then the quality of the body of the evidence was lowered by one level. If results were consistent, then the quality of the body of the evidence was left at the original level. Similarly, if there was reporting bias (publication bias), then the quality of the body of evidence would be lowered by one level.

Quality of evidence across the studies for each main outcome

RCT	Quality of the evidence	Observational studies
No serious flaws in study quality	High	Extremely strong association and no threats to validity
Serious flaws in design or execution or quasi-experimental design	Intermediate	Strong and consistent association and no plausible confounders
Very serious flaws in design or execution	Low	No serious flaws in study quality
Very serious flaws and at least one other serious threat to validity	Very low	Serious flaws in design and execution

Additional factors that lower study quality are important inconsistency of results, some uncertainty about directness, high probability of reporting bias and sparseness of data. Major uncertainty about directness can lower the quality by two levels

Additional factors that may increase quality of observational studies are all plausible residual confounding, if present, that would reduce the observed effect and evidence of a dose–response gradient

Adapted from Judging Confidence: Guidelines for Grading Evidence and Recommendations. Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group. Draft, January 2003.

References

[1] Ashley-Koch A, Yang Q, Olney RS. Sickle hemoglobin (Hb S) allele and sickle cell disease: a HuGE review. Am J Epidemiol 2000;151:839–45.

[2] Freie HM. Sickle cell diseases and hormonal contraception. Acta Obstet Gynecol Scand 1983;62:211–7.

[3] National Institutes of Health (NIH), National Heart, Lung, and Blood Institute. Facts about sickle cell anemia. Rockville, (MD): National Institutes of Health; 2004.
[4] Fort AT, Morrison JC, Diggs LW, Fish SA, Berreras L. Counseling the patient with sickle cell disease about reproduction: pregnancy outcome does not justify the maternal risk. Am J Obstet Gynecol 1971;111:324–7.
[5] Sun PM, Wilburn W, Raynor BD, Jamieson D. Sickle cell disease in pregnancy: twenty years of experience at Grady Memorial Hospital, Atlanta, Georgia. Am J Obstet Gynecol 2001;184: 1127–30.
[6] Howard RJ, Tuck SM. Contraception and sickle cell disease. IPPF Med Bull 1994;28:3–4.
[7] Lutcher CL. Blood coagulation studies and the effect of oral contraceptives in patients with sickle cell anemia. Clin Res Southern Soc Hematol 1976;24:47a.
[8] Evans DK. Sickle cells and hormonal contraception. Br J Fam Plann 1984;10:80–1.
[9] World Health Organization. Medical eligibility criteria for contraceptive use. 3rd ed. Geneva: World Health Organization; 2004.
[10] Koshy M. Sickle cell disease and pregnancy. Blood Rev 1995; 9:157–64.
[11] Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
[12] Ladipo OA, Falusi AG, Feldblum PJ, Osotimehin BO, Otolorin EO, Ojengbede OA. Norplant use by women with sickle cell disease. Int J Gynecol Obstet 1993;41:85–7.
[13] Barbosa IC, Ladipo OA, Nascimento ML, et al. Carbohydrate metabolism in sickle cell patients using a subdermal implant containing nomegestrol acetate (Uniplant). Contraception 2001; 63:263–5.
[14] Nascimento ML, Ladipo OA, Coutinho E. Nomegestrol acetate contraceptives implant use by women with sickle cell disease. Clin Pharmacol Ther 1998;64:433–8.
[15] de Abood M, de Castillo Z, Guerrero F, Espino M, Austin KL. Effect of Depo-Provera or Microgynon on the painful crises of sickle cell anemia patients. Contraception 1997;56:313–6.
[16] De Ceulaer K, Gruber C, Hayes R, Serjeant GR. Medroxyprogesterone acetate and homozygous sickle-cell disease. Lancet 1982; 2:229–31.
[17] Yoong WC, Tuck SM, Yardumian A. Red cell deformability in oral contraceptive pill users with sickle cell anaemia. Br J Haematol 1999;104:868–70.
[18] Howard RJ, Lillis C, Tuck SM. Contraceptives, counselling, and pregnancy in women with sickle cell disease. BMJ 1993; 306:1735–7.
[19] Adadevoh BK, Isaacs WA. The effect of megestrol acetate on sickling. Am J Med Sci 1973;265:367–70.