Pregnancy in the Sickle Cell Disease and Fetomaternal Outcomes in Different Sickle cell Genotypes: A Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND: Pregnancy is a major concern among women with the sickle cell disease (SCD), and it is associated with increased adverse outcomes. The aim of the present meta-analysis is to report the fetomaternal outcomes in different sickle cell genotypes.

METHODS: In this systematic review and meta-analysis, a comprehensive search of databases and search engines such as PubMed, Scopus, Web of Science, ProQuest, Cochrane Library, Science Direct and Google Scholar were performed. Any observational studies that had compared at least one outcome such as maternal outcomes, fetal outcomes, and morbidity between two groups of pregnant women with different types of sickle cell genotypes and pregnant women without SCD were evaluated.

RESULTS: A total number of 9,827 pregnant women with SCD were examined. The results showed that pregnancy in SCD increased the risk of adverse outcomes for the mothers (including postpartum hemorrhage, prematurity, pregnancy-induced hypertension, pre-eclampsia, eclampsia, cesarean section, lower segment cesarean section, maternal death), fetus (including live births, low birth weight, intrauterine growth restriction, APGAR score at 5 min <7, stillbirth, neonatal death, perinatal mortality, acute fetal distress, intrauterine fetal death) and morbidity among the SCD (severe anemia, urinary tract infection, blood transfusion, painful crises, acute chest syndrome, vaso-occlusive crises).

CONCLUSION: According to the results of this meta-analysis, pregnancy in the SCD is associated with an increased risk of maternal outcomes, fetal outcomes, and morbidity among SCD patients with different genotypes. Pregnancy in sickle cell hemoglobinopathies needs careful multidisciplinary management and cautious caring so as to decrease maternal and fetal morbidity and mortality.

KEYWORDS: Anemia, Sickle Cell, Pregnancy, Fetus, Pregnancy Complications, Meta-Analysis
INTRODUCTION

Sickle cell disease (SCD), caused by a mutation in the β-globin gene HBB, is the most inherited condition and is common in South African Sahara desert, South America, Central America, Saudi Arabia, India and Mediterranean countries (1). The predominant genotypes that give rise to SCD include Hb SS, Hb SC, Hb Sβ+-thalassemia and Hb Sβ0-thalassemia. Other rare forms include hemoglobin SD and hemoglobin SE (2). SCD is perceived as a global threat by World Health Organization (WHO) and about 5% of the world population and more than 7% of pregnant women worldwide suffer from hemoglobinopathies such as SCD (2-3). The adverse effects of this disease are serious infections, damage to vital body organs, brain stroke, renal disease, respiratory problems, bone marrow suppression, failure to thrive (FTT), cognitive disorder, delayed maturation in children and the high rate of maternal and fetal mortalities (3-4).

Many studies have shown that SCD is negatively associated with maternal health and prenatal conditions. The fetomaternal consequences of SCD are complicated. The main maternal complications of pregnancies complicated by SCD anemia, infection, vaso-occlusive crisis, preeclampsia, preterm labor and the higher risk of the cesarean. The fetal problems that can affect perinatal outcomes are intrauterine growth restriction, premature birth, abnormal fetal heart rate and intrauterine fetal death. A high rate of maternal and fetal death has been reported in pregnant women with SCD than the healthy population (4-6). As already explained, this disease is accompanied by lifelong adverse effects and preterm mortality. Thus, a higher quality of taking care of people with SCD can improve survival and, thus, the number of fertile women (5). It has been previously shown that SCD can increase complications during pregnancy and in turn negatively influence pregnancy outcomes. However, the inherent heterogeneity of SCD pathophysiology in adjusting these studies can reduce trust in estimating the pregnancy risks of this disease (6-7). Insufficient information about the outcomes of this disease, with different genotypes, among pregnant women poses challenges in prenatal consultations and developing guideline recommendations based on the available evidence to provide comprehensive prenatal care services. Thus, the present systematic review and meta-analysis helps to explore the maternal and fetal outcomes of different genotypes of SCD taking into account the factors that might cause heterogeneity in the existing body of research evidence.

METHODS

The present study was conducted based on the preferred reporting items for systematic review and meta-analysis (PRISMA) checklist (8), but was not registered in the international prospective register of systematic reviews (PROSPERO) database and a public protocol does not exist. No ethical approval was sought for this systematic review. As this study is a systematic review of previously published studies, the need for ethics approval and patient informed consent was therefore waived. The components of structured question (PICO) were population (P): pregnant women with different types of sickle cell genotypes; and intervention (I): not required; comparison (C): with healthy pregnant women with HbAA; outcome (O): maternal outcomes, fetal outcomes, and morbidity in the SCD.

Search strategy: A comprehensive and regular search was done from inception to 14 December 2021, with the keywords (“Anemia, Sickle Cell” [MeSH]) AND (“Pregnancy” [MeSH] OR “Pregnant Women” [MeSH] OR “Fetus” [MeSH] OR “Obstetrics” [MeSH] OR “Pregnancy Complications” [MeSH]) without time and language restrictions in the following databases: Web of Science, Scopus, ProQuest, Cochrane Library, Science Direct, Medline, MEDLINE/PubMed and Google Scholar search engine. Also, the reference list of included studies was hand-searched for any relevant studies missing in the database searches. Prior to the search, it was decided that gray literature would not be searched as these studies are not peer-reviewed and lacks quality control. Four weeks before we submitted the final manuscript to the journal, we performed an updated search on all specified databases.
Eligibility criteria: Any historical cohort, prospective cohort, retrospective cross-sectional, and retrospective case-control, observational case-control, descriptive studies with two comparators and descriptive cross-sectional studies, that had compared at least one outcome such as (maternal outcomes, fetal outcomes, and morbidity in the SCD) between two groups of pregnant women with different types of sickle cell genotypes and pregnant women without SCD were included in this systematic review and meta-analysis. Clinical trials, quasi-experimental studies, reviews, letter to editors, or case reports or those reporting outcomes in only one group or in non-pregnant women were excluded from this systematic review and meta-analysis.

Selection procedure: EndNote X8 software was used to manage the included studies. Out of a total number of 3266 search, 450 texts were excluded due to duplication. Then, the titles of 2,816 texts were reviewed and 1,707 texts that were not related to the topic were excluded. The abstracts of 1,109 texts were reviewed and 900 texts that were not related to the aims were excluded. The full text of 209 studies was reviewed by two researchers (M.A & A.P) based on the inclusion and exclusion criteria. 148 studies were excluded due to the lack of a detailed reporting of findings in the two comparison groups; 4 were excluded due to the report of findings in non-pregnant women; 3 studies were excluded as they were systematic reviews, and 7 studies were so due to the use of randomization clinical trials. Finally, 47 studies were selected and they entered the quality evaluation stage (Figure 1).

Quality assessment: The Joanna Briggs Institute (JBI) Critical Appraisal 5-item Checklist was used for quality assessment of included studies (case-control studies and longitudinal cohort, or cross-sectional studies reporting the prevalence data) (9). The two authors independently reviewed each study based on the criteria in these checklists with the options of “Yes”, “No”, and “Unclear”. For
Depending on the outcome under consideration, comparison was at least 3, the analys if the number of studies in each reference group was women with SCT, HbAA, SCD, SCT, HbSS, HbSC. In each analysis, the comparisons were made for women with the total numbers of pregnancies and events. Separate unadjusted risk ratio, calculated from the given maternal and pregnancy outcome was the measure of the effect of maternal SCD on fetal morbidity among the SCD including (severe anemia, urinary tract infection (UTI), blood transfusion (BT), painful crisis, acute chest syndrome, vaso occlusive crises (VOC) were collected for each study. We obtained the gross national income per capita for each study from the World Bank data.

Data extraction: The data extraction was carried out independently by 2 authors (M.A. and A.P.) using a standard extraction form. The following information was extracted from each study: authors’ names; year of publication; title; design; setting; the number of women in exposed and comparator groups; genotype; and outcomes. For each study, the required data were retrieved for the meta-analysis on the outcomes of interest: maternal outcomes such as premature rupture of membranes (PROM), postpartum hemorrhage (PPH), prematurity, pregnancy-induced hypertension (PIH), pre-eclampsia, eclampsia, gestational diabetes mellitus, cesarean section, lower segment caesarean section (LSCS), maternal death) and fetal outcomes. including (mean birth weight, live births, low birth weight (LBW), intrauterine growth restriction (IUGR).

APGAR score at 5 min <7, stillbirth, neonatal death, perinatal mortality, acute fetal distress (AFD), intra-uterine fetal death (IUFD), and morbidity among the SCD including (severe anemia, urinary tract infection (UTI), blood transfusion (BT), painful crisis, acute chest syndrome, vaso occlusive crises (VOC) were collected for each study. We obtained the gross national income per capita for each study from the World Bank data.

Data synthesis and statistical analysis: The analyses were pregnancy based. The main measure of the effect of maternal SCD on fetomaternal and pregnancy outcome was the unadjusted risk ratio, calculated from the given numbers of pregnancies and events. Separate comparisons were made for women with the total SCD, SCT, HbSS, HbSC. In each analysis, the reference group was women with SCT, HbAA, HbSC. If the number of studies in each comparison was at least 3, the analysis was done. Depending on the outcome under consideration, studies with no events in either arm were excluded. The pooled risk ratio was reported with 95% of confidence interval (95% CI). Besides, the randomized model was reported by 95% CI. A p-value < 0.05 was considered statistically significant. The Q statistic and the I² index were used to assess the heterogeneity of the studies. The I² index was used due to its accuracy to compensate for the lack of power (the Q statistic) in small sample sizes or increase the power in large sample sizes. In the I² index, a value below 50% indicated a low variance in the studies. Moreover, a fixed effect model and the inverse variance method were used. Otherwise, instrumental variable (IV) heterogeneity method was used (10). Where substantial heterogeneity existed (by I²), mixed-effects analysis was used to test the study differences using the following variables: quality of study reporting; country gross national income (GNI), and the year of publication. The results are summarized as odds ratios. All statistical analyses were done in the Comprehensive Meta-analysis (version 2) and Rev-Man (version 5.3).

RESULTS

Characteristics of the included studies: In 47 studies published between 1977 and 2020, a total number of 9,827 pregnant women with SCD, 9,734,709 pregnant women with HbAA, 3,298 pregnant women with SCT, 730 pregnant women with HbSC, and 1,691 pregnant women with HbSS were examined. The pooled mean age of pregnant women in SCD according to 12 studies was 25.97 ± 4.8; HbAA according to 17 studies was 26.93 ± 5.49; SCT according to 4 studies was 26.59 ± 5.52; HbSC according to 5 studies was 27.12 ± 12.36 and HbSS according to 9 studies was 25.97 ± 5.49. The mean age of pregnant women did not show any statistically significant difference in any of the comparison groups (SCD vs HbAA) (SMD: -0.1, 95% CI: -0.2, 0.033), (SCD vs. SCT) (SMD: -0.23, 95% CI: -0.5, 0.09), (HbSS vs. HbAA) (SMD: -0.08, 95% CI: -0.2, 0.04), (HbSS vs. HbSC) (SMD: -0.07, 95% CI: -0.2, 0.1). In this review, the total sample size of selected studies was variable from 50 to 8821321. The other information about the selected studies is listed in Table 1.
Table 1: Basic characteristics of the studies included in the meta-analysis.

| First author and year of publication | Country            | Country gross national income | Study design          | Sample size | Quality of study reporting |
|--------------------------------------|--------------------|-------------------------------|-----------------------|-------------|----------------------------|
| Nkwabong, 2020[11]                  | Cameroon           | Lower-middle income          | Historical cohort     | 120         | Moderate                   |
| Galiba, 2020[12]                    | Congo              | Lower-middle income          | Historical cohort     | 195         | Moderate                   |
| Wellenstein, 2019[13]               | United States      | High-income                  | Historical cohort     | 31840       | High                       |
| Oppong, 2019[14]                    | Ghana              | Lower-middle income          | Prospective cohort    | 266         | High                       |
| Nwafor, 2019[15]                    | Nigeria            | Lower-middle income          | Retrospective case-control | 488       | Moderate                   |
| Kumar Dora, 2019[16]                | India              | Lower-middle income          | Prospective observational case-control | 178        | Moderate                   |
| Kose, 2019[17]                      | India              | Lower-middle income          | Descriptive cross-sectional | 114        | Moderate                   |
| Haseeb, 2019[18]                    | Saudi Arabia       | High-income                  | Historical cohort     | 902         | High                       |
| Girish Mahajan, 2019[19]            | India              | Lower-middle income          | Prospective cohort    | 180         | High                       |
| Babah, 2019[20]                     | Nigeria            | Lower-middle income          | Prospective cohort    | 100         | High                       |
| Jyoti Kar, 2018[21]                 | India              | Lower-middle income          | Prospective case-control | 2040       | Moderate                   |
| Gaddikeri, 2017[22]                 | India              | Lower-middle income          | Prospective case-control | 108        | Moderate                   |
| Desai, 2017[1]                      | India              | Lower-middle income          | Case control          | 10036       | High                       |
| DCouth, 2017[23]                    | India              | Lower-middle income          | Retrospective cohort  | 143         | Moderate                   |
| Fouedjio, 2016[24]                  | Cameroon           | Lower-middle income          | Retrospective case-control | 128        | High                       |
| Elenga, 2016[25]                    | Brazil             | Upper-middle income          | Retrospective case-control | 119        | High                       |
| al-Jufairi, 2016[26]                | Bahrain            | High-income                  | Retrospective Case-Control | 370        | High                       |
| Oteng-Ntim, 2015[27]                | United Kingdom     | High-income                  | Prospective cohort    | 266496      | High                       |
| Costa, 2015[28]                     | Brazil             | Upper-middle income          | Prospective cohort    | 312         | Moderate                   |
| Adama-Hondéglà, 2015[29]            | Togo               | Low-middle income            | Descriptive and retrospective | 226        | High                       |
| Silva-Pinto, 2014[30]               | Brazil             | Upper-middle income          | Historical cohort     | 61          | High                       |
| Natu, 2014[31]                      | India              | Lower-middle income          | Historical cohort     | 579         | High                       |
| Alayed, 2014[32]                    | Canada             | High-income                  | Historical cohort     | 8821321     | High                       |
| Zia, 2013[33]                       | Saudi Arabia       | High-income                  | Historical cohort     | 112         | Moderate                   |
| Thame, 2013[34]                     | Jamaica            | Upper-middle income          | Prospective cohort    | 82          | Moderate                   |
| Muganyizi, 2013[35]                 | Tanzania           | Lower-middle income          | Historical cohort     | 155356      | Moderate                   |
| Daugavina, 2013[36]                 | India              | Lower-middle income          | Prospective cohort    | 160         | Moderate                   |
| Boulet, 2013[37]                    | United States      | High-income                  | Historical cohort     | 335348      | High                       |
| Acharya, 2013[38]                   | India              | Lower-middle income          | Case control          | 50          | High                       |
| Wilson, 2012[39]                    | Ghana              | Lower-middle income          | Historical            | 1103        | High                       |
| Al Kahtani, 2012[40]                | Saudi Arabia       | High-income                  | Historical cohort     | 1176        | Moderate                   |
| Nomura, 2010[41]                    | Brazil             | Upper-middle income          | Historical cohort     | 107         | Moderate                   |
| Ngô, 2010[42]                       | France             | High-income                  | Historical cohort     | 384         | High                       |
| Barfield, 2010[43]                  | United States      | High-income                  | Historical cohort     | 115823      | Moderate                   |
| Al Jama, 2009[44]                   | Saudi Arabia       | High-income                  | Historical cohort     | 755         | Moderate                   |
| Afolabi, 2009[45]                   | Nigeria            | Lower-middle income          | Historical cohort     | 225         | Moderate                   |
| Ashish, 2008[46]                    | India              | Lower-middle income          | Case control          | 224         | Moderate                   |
| Thame, 2007[47]                     | Jamaica            | Upper-middle-income          | Historical cohort     | 252         | Moderate                   |
| Rajab, 2006[48]                     | Bahrain            | High-income                  | Historical cohort     | 662         | Moderate                   |
| Serjeant, 2005[49]                  | Jamaica            | Upper-middle-income          | Prospective cohort    | 535         | Moderate                   |
| Serjeant, 2004[50]                  | Jamaica            | Upper-middle-income          | Prospective cohort    | 120         | Moderate                   |
| Sun, 2001[51]                       | United States      | High-income                  | Historical cohort     | 509         | Moderate                   |
| Al Mulhim, 2000[52]                 | Saudi Arabia       | High-income                  | Historical cohort     | 198         | Moderate                   |
| Balgir, 1997[53]                    | India              | Lower-middle income          | Historical cohort     | 190         | Moderate                   |
| Howard, 1995[54]                    | United Kingdom     | High-income                  | Historical cohort     | 250         | Moderate                   |
| Dare, 1992[55]                      | Nigeria            | Lower-middle income          | Historical cohort     | 142         | Moderate                   |
| Blattner, 1977[56]                  | United States      | High-income                  | Prospective cohort    | 170         | Moderate                   |
Table 2: Details of comparing maternal outcomes in women with SCD (based on different sickle cell genotypes) vs. women with no SCD.

| Maternal outcomes | Case-Control | Number of studies | Outcome among group1 | Outcome among group2 | 95% confidence interval (95% CI) | P-Value | Heterogeneity | I Squared% | Egger P-Value |
|-------------------|--------------|-------------------|---------------------|---------------------|---------------------------------|---------|---------------|------------|---------------|
| PROM              | Group 1      | 5                 | 167/4837            | 336851 / 8818198    | [0.4 - 2.9]                     | 0.84    | 4             | <0.0001   | 86            | 0.63          |
| SCD               | AA           | 7                 | 119/2022           | 10422 / 337118      | [1.2 - 8]                       | 0.01    | 6             | <0.0001   | 90            | 0.31          |
| SCD               | SC           | 6                 | 33/292             | 29/310              | [0.53 - 2.7]                    | 0.64    | 5             | 0.051 validity | 53            | 0.84          |
| SCT               | AA           | 3                 | 12/162             | 42 / 2496           | [0.36 - 24.1]                   | 0.3     | 2             | <0.0001   | 88            | 0.53          |
| Prematurity       | SCD          | AA 17             | 910/4074           | 153911 / 873535     | [1.6 - 2.3]                     | <0.0001 | 16            | <0.0001   | 69            | 0.08          |
|                   | SCT          | 8                 | 205 / 1335         | 2596 / 34407        | [0.9 - 4.8]                     | 0.08    | 7             | <0.0001   | 94            | 0.53          |
|                   | SS           | 16                | 308 / 1116         | 50217/270758        | [2.1 - 5.3]                     | <0.0001 | 15            | <0.0001   | 90            | 0.73          |
|                   | SC           | 10                | 209/637            | 129/615             | [1.1 - 2.3]                     | 0.003   | 9             | <0.0001   | 57            | 0.43          |
| PIH               | SCD          | AA 4              | 57 / 722           | 711 / 9118          | [0.7-3.6]                       | 0.18    | 3             | 0.01       | 70            | 0.85          |
|                   | SCT          | 3                 | 13 / 245           | 143 / 1749          | [0.3 - 1.8]                     | 0.5     | 2             | 0.27       | 22            | 0.71          |
|                   | SS           | AA 3              | 275 / 2579         | 4476 / 41174        | [0.96 - 2.7]                    | 0.06    | 2             | <0.0001   | 91            | 0.3           |
|                   | SS           | AA 6              | 108 / 735          | 77 / 3592           | [1.6 - 1.45]                    | 0.004   | 5             | <0.0001   | 92            | 0.59          |
|                   | SS           | SC 4              | 43 / 374           | 22 / 317            | [0.5 - 3.7]                     | 0.4     | 3             | 0.04       | 63            | 0.91          |
| Pre-eclampsia     | SCD          | AA 9              | 575 / 5805         | 291915 / 8934162    | [1.5 - 2.9]                     | <0.0001 | 8             | <0.0001   | 75            | 0.15          |
|                   | SCT          | 3                 | 41 / 124           | 26 / 205            | [1.3 - 6.6]                     | 0.008   | 2             | 0.07       | 62            | 0.81          |
|                   | SS           | AA 3              | 28 / 160           | 163 / 610           | [0.4 - 1.9]                     | 0.8     | 2             | 0.14       | 48            | 0.77          |
|                   | SS           | AA 10             | 114 / 987          | 78 / 2167           | [2.1 - 3.8]                     | <0.0001 | 9             | 0.69       | 0             | 0.79          |
|                   | SS           | SC 9              | 77 / 699           | 56 / 664            | [0.8 - 1.8]                     | 0.3     | 8             | 0.32       | 13            | 0.15          |
| Eclampsia         | SCD          | AA 11             | 267 / 7652         | 33941 / 12276629    | [1.1 - 6.4]                     | 0.025   | 10            | <0.0001   | 94            | 0.64          |
|                   | SCT          | 3                 | 9 / 196            | 20 / 1731           | [0.8 - 5.6]                     | 0.09    | 2             | 0.64       | 0             | 0.73          |
|                   | SS           | AA 6              | 20 / 508           | 13 / 1354           | [1.4 - 10]                      | 0.006   | 5             | 0.22       | 25            | 0.03          |
|                   | SS           | SC 4              | 22 / 389           | 23 / 433            | [0.7 - 2.4]                     | 0.3     | 7             | 0          | 0             | 0.45          |
| GDM               | SCD          | AA 3              | 52 / 799           | 91 / 1661           | [0.8 - 1.6]                     | 0.4     | 2             | 0.6        | 0             | 0.65          |
| Cesarean section  | SCD          | AA 16             | 1539 / 4279        | 178281 / 615649     | [1.5 - 2.2]                     | <0.0001 | 15            | <0.0001   | 91            | 0.06          |
|                   | SCT          | 4                 | 88 / 296           | 158 / 1805          | [0.7 - 2.6]                     | 0.2     | 3             | <0.0001   | 86            | 0.73          |
|                   | SS           | AA 9              | 327 / 959          | 463 / 2163          | [1.4 - 2.1]                     | <0.0001 | 8             | 0.01       | 57            | 0.35          |
|                   | SS           | SC 8              | 247 / 648          | 259 / 620           | [0.8 - 1.8]                     | 0.7     | 7             | 0.07       | 46            | 0.1           |
| LSCS              | SCD          | AA 3              | 70 / 199           | 53 / 284            | [0.9 - 4.5]                     | 0.1     | 2             | 0.01       | 75            | 0.48          |
|                   | SCT          | 3                 | 68 / 177           | 61 / 221            | [1.4 - 2]                       | 0.06    | 2             | 0.02       | 72            | 0.14          |
|                   | SS           | AA 3              | 40 / 140           | 49 / 2051           | [0.93 - 4.1]                    | 0.059   | 2             | <0.0001   | 91            | 0.58          |
|                   | SS           | AA 4              | 82 / 201           | 109 / 2193          | [1.04 - 13]                     | 0.04    | 3             | <0.0001   | 96            | 0.65          |
| Maternal death    | SCD          | AA 9              | 40 / 5536          | 1579 / 8974283      | [3.7 - 19]                      | <0.0001 | 8             | <0.0001   | 71            | 0.27          |
|                   | SS           | AA 4              | 12 / 179           | 0 / 2266            | [6 - 222]                       | <0.0001 | 3             | 0.2        | 30            | 0.71          |

PROM: Premature rupture of membranes, PPH: Postpartum hemorrhage, PIH: Pregnancy-induced hypertension, GDM: Gestational diabetes mellitus, LSCS: Lower segment caesarean section, SCD: Sickle cell disease, SCT: Sickle cell trait
Association between SCD and maternal outcome: The increased risk of PROM was not statistically significant in pregnant women with SCD vs HbAA based on 5 studies (RR: 1.1, 95% CI: 0.4, 2.9). The increased risk of PPH was statistically significant in pregnant women with SCD vs HbAA based on 7 studies (RR: 3.2, 95% CI: 1.2, 8). The increased risk of prematurity was statistically significant in pregnant women with SCD vs HbAA based on 7 studies (RR: 3.2, 95% CI: 1.2, 8) and HbSS vs. HbAA based on 16 studies (RR: 2.9, 95% CI: 1.6, 4.6) SCD vs. SCT based on 5 studies (RR: 1.7, 95% CI: 1.1, 2.5), SCT vs. HbAA based on 5 studies (RR: 3, 95% CI: 0.9, 9.3) and HbSS vs. HbAA based on 4 studies (RR: 11.8, 95% CI: 2.5, 54.5). The increased risk of eclampsia was statistically significant in pregnant women with SCD vs HbAA based on 11 studies (RR: 2.8, 95% CI: 1.1, 6.4) and HbSS vs. HbAA based on 6 studies (RR: 3.8, 95% CI: 1.4, 10). The increased risk of gestational diabetes mellitus (GDM) was not statistically significant in pregnant women with SCD vs. HbAA based on 3 studies (RR: 1.1, 95% CI: 0.8, 1.6) and SCD vs. SCT based on 3 studies (RR: 0.56, 95% CI: 0.1, 2.1). The increased risk of cesarean section was statistically significant in pregnant women with SCD vs. HbAA based on 6 studies (RR: 3.7, 95% CI: 1.04, 13). The increased risk of maternal death was statistically significant in pregnant women with SCD vs. HbAA based on 9 studies with (RR: 7.2, 95% CI: 3.7, 19) and HbSS vs. HbAA based on 4 studies (RR: 37, 95% CI: 6, 222). The details of the analysis are reported in Table 2.

Association between SCD and fetal outcome: The decrease of live births was statistically significant in pregnant women with SCD vs. HbAA based on 5 studies (RR: 0.8, 95% CI: 0.7, 0.9) and HbSS vs. HbAA based on 5 studies (RR: 0.7, 95% CI: 0.7, 0.9). The increased risk of LBW was statistically significant in pregnant women with SCD vs. HbAA based on 11 studies (RR: 2.8, 95% CI: 1.6, 4.6), SCD vs. SCT based on 5 studies (RR: 1.7, 95% CI: 1.1, 2.5), SCT vs. HbAA based on 5 studies (RR: 3, 95% CI: 0.9, 9.3) and HbSS vs. HbAA based on 4 studies (RR: 11.8, 95% CI: 2.5, 54.5). The increased risk of IUGR was statistically significant in pregnant women with SCD vs AA based on 10 studies (RR: 2.3, 95% CI: 1.6, 3), HbSS vs. HbAA based on 6 studies (RR: 2.8, 95% CI: 1.1, 2.9), and in the group with SCD vs SCT based on 3 studies (RR: 2.9, 95% CI: 1.3, 6.6) and HbSS vs. HbAA based on 10 studies (RR: 2.8, 95% CI: 2.1, 3.8). The increased risk of stillbirth was statistically significant in pregnant women with SCD vs. HbAA based on 9 studies (RR: 5.7, 95% CI: 3.0, 10) and HbSS vs. HbAA based on 10 studies (RR: 10.8, 95% CI: 6.1, 10). The increased risk of neonatal death was statistically significant in pregnant women with SCD vs. HbAA based on 9 studies (RR: 5.7, 95% CI: 3.0, 10) and HbSS vs. HbAA based on 10 studies (RR: 10.8, 95% CI: 6.1, 10). The increased risk of AFD was statistically significant in pregnant women with SCD vs. HbAA based on 6 studies (RR: 2.2, 95% CI: 1.4, 4.5) and HbSS vs. HbAA based on 6 studies (RR: 2.9, 95% CI: 1.4, 5.8). The increased risk of perinatal mortality was statistically significant in pregnant women with SCD vs. HbAA based on 7 studies (RR: 3.3, 95% CI: 2.2, 5), and in the group with SCD vs. SCT based on 5 studies (RR: 2.8, 95% CI: 1.1, 2.9). The increased risk of IUFD was statistically significant in pregnant women with HbSS vs. HbAA based on 5 studies (RR: 2.8, 95% CI: 1.1, 2.9). The details of the analysis are reported in Table 3.
Table 3: Details of comparing fetal outcomes in women with SCD (based on different sickle cell genotypes) vs. women with no SCD.

| Fetal outcomes | Case-Control | Number of studies | Outcome among group 1 | Outcome among group 2 | Pooled risk ratio | 95% confidence interval (95% CI) | P-Value | Heterogeneity | Egger P-Value |
|----------------|--------------|-------------------|-----------------------|-----------------------|------------------|---------------------------------|---------|---------------|---------------|
| Live births    | SCD AA 5     | 683 / 830         | 1618 / 1701           | 0.8                   | 0.7-0.9          | <0.000                          | 4       | 0.009         | 9             | 0.00          |
|                | SCD SCT 3    | 88 / 107          | 113 / 130             | 0.94                  | 0.8-1.1          | 0.46                            | 2       | 0.06          | 64            | 0.56          |
|                | SS AA 5      | 243 / 331         | 643 / 678             | 0.7                   | 0.7-0.9          | <0.000                          | 4       | 0.01          | 68            | 0.23          |
| Low birth weight | SCD AA 11   | 425 / 194         | 35322 / 546396        | 2.8                   | 1.6-4.6          | <0.000                          | 10      | <0.000        | 96            | 0.19          |
|                | SCD SCT 5    | 197 / 355         | 790 / 1924            | 1.7                   | 1.1-2.5          | 0.005                           | 4       | 0.001         | 75            | 0.83          |
|                | SCT AA 5     | 806 / 1861        | 3873 / 10393          | 3                     | 0.9-9.3          | 0.04                            | 4       | <0.000        | 97            | 0.13          |
|                | SS AA 4      | 58 / 193          | 1936 / 268448         | 11.8                  | 2.5-54.5         | 0.001                           | 3       | <0.000        | 97            | 0.23          |
|                | SS SC 4      | 102 / 315         | 89 / 360              | 1                     | 0.5-3.2          | 0.54                            | 3       | <0.000        | 90            | 0.73          |
| IUGR           | SCD AA 10    | 407 / 6359        | 157425 / 894299       | 2.3                   | 1.6-3            | <0.000                          | 9       | <0.000        | 75            | 0.32          |
|                | SCD SCT 4    | 46 / 377          | 65 / 1851             | 1.1                   | 0.4-3.3          | 0.76                            | 3       | 0.001         | 81            | 0.68          |
|                | SCT AA 4     | 63 / 1872         | 151 / 10373           | 3.5                   | 0.9-13           | 0.03                            | 3       | <0.000        | 89            | 0.22          |
|                | SS AA 6      | 102 / 587         | 54 / 3483             | 7.3                   | 3.5-15           | <0.000                          | 5       | 0.003         | 72            | 0.24          |
| Apgar score at 5 min < 7 | SCD AA 6    | 108 / 917        | 23103 / 156248        | 1.9                   | 1.3-2.6          | <0.000                          | 5       | 0.18          | 33            | 0.5           |
| Stillbirth     | SS SC 4      | 61 / 324          | 36 / 392              | 1.4                   | 0.65-3           | 0.35                            | 3       | 0.06          | 58            | 0.8           |
|                | SCD AA 6     | 108 / 917        | 23103 / 156248        | 1.9                   | 1.3-2.6          | <0.000                          | 5       | 0.18          | 33            | 0.5           |
|                | SS SC 4      | 22 / 345          | 27 / 585              | 1.7                   | 0.7-3.9          | 0.16                            | 4       | 0.12          | 45            | 0.1           |
| Neonatal death | SCD AA 9     | 116 / 140         | 12550 / 4238          | 5.7                   | 3-10             | <0.000                          | 8       | 0.02          | 55            | 0.53          |
|                | SCT AA 4     | 9 / 280           | 4 / 302               | 2.2                   | 0.6-6.8          | 0.18                            | 3       | 0.96          | 0             | 0.95          |
|                | SS AA 10     | 74 / 893          | 343 / 267740          | 10.8                  | 6.1-19           | <0.000                          | 9       | 0.83          | 0             | 0.2           |
|                | SS SC 6      | 36 / 373          | 31 / 429              | 1.3                   | 0.7-2.5          | 0.4                             | 5       | 0.27          | 20            | 0.91          |
| Perinatal mortality | SCD AA 6   | 30 / 1120        | 19 / 1893             | 2.2                   | 1.4-4.5          | 0.003                           | 5       | 0.76          | 0             | 0.54          |
|                | SS SC 6      | 23 / 1231         | 13 / 1231             | 2.9                   | 1.4-5.8          | 0.005                           | 5       | 0.52          | 0             | 0.3           |
| AFD            | SCD AA 7     | 95 / 1297         | 132 / 10866           | 3.3                   | 2.2-5            | <0.000                          | 6       | 0.37          | 6             | 0.16          |
|                | SS AA 3      | 32 / 246          | 113 / 11173           | 8.6                   | 0.7-10           | 0.08                            | 2       | <0.000        | 90            | 0.82          |
|                | SS SC 4      | 23 / 732          | 13 / 1231             | 2.9                   | 1.4-5.8          | 0.005                           | 5       | 0.52          | 0             | 0.3           |
| IUFD           | SCD AA 5     | 78 / 4414         | 408 / 881785          | 11.4                  | 0.9-14           | 0.057                           | 4       | <0.000        | 97            | 0.04          |
|                | SCT AA 3     | 6 / 162           | 14 / 637              | 2.6                   | 1-7              | 0.05                            | 2       | 0.8           | 0             | 0.7           |
|                | SS AA 4      | 7 / 139           | 2 / 307               | 5.4                   | 1.3-22.7         | 0.01                            | 3       | 0.4           | 0             | 0.21          |
|                | SS SC 3      | 8 / 193           | 15 / 280              | 1.1                   | 0.16-8.2         | 0.87                            | 2       | 0.8           | 60            | 0.77          |

IUGR: Intrauterine growth restriction, AFD: Acute fetal distress, IUFD: Intra-uterine fetal death
Association between SCD and morbidity: The increased risk of severe anemia was statistically significant in pregnant women with HbSS vs. HbAA based on 4 studies (RR: 29, 95% CI: 4, 203). The increase risk of UTI was statistically significant in pregnant women with SCD vs. HbAA based on 7 studies (RR: 2.1, 95% CI: 1.8, 2.4) and HbSS vs. HbAA based on 10 studies (RR: 5.1, 95% CI: 2.1, 12.4). The increased risk of BT was statistically significant in pregnant women with SCD vs. HbAA based on 4 studies (RR: 29, 95% CI: 4, 26). The increased risk of acute chest syndrome was statistically significant in pregnant women with HbSS vs. HbAA based on 3 studies (RR: 117.1, 95% CI: 23.4, 586). The increased risk of acute chest syndrome was statistically significant in pregnant women with HbSS vs. HbAA based on 4 studies with (RR: 33, 95% CI: 7.5, 137.5). The increased risk of VOC was statistically significant in pregnant women with HbSS vs. HbAA based on 3 studies (RR: 47.6, 95% CI: 9.2, 245.2). The details of the analysis are reported in Table 4.

**Table 4:** Details of comparing morbidity women with SCD (based on different sickle cell genotypes) vs. women with no SCD.

| Morbidity among the sickle cell disease | Case-Control Group | Number of studies | Outcome among group 1 | Outcome among group 2 | Poole d risk ratio | 95% confidence interval (95% CI) | P-Value | Heterogeneity | Egge Value |
|----------------------------------------|--------------------|-------------------|-----------------------|-----------------------|--------------------|----------------------------------|---------|--------------|-------------|
| Severe Anemia                          | SCD                | 3                 | 21 / 141              | 14 / 189              | 1.2                | [0.1-9]                          | 0.8     | 2            | 0.002       |
| UTI                                    | SCD                | 4                 | 22 / 169              | 5 / 219               | 29                 | [4-203]                          | 0.001   | 3            | 0.02        |
|                                         | AA                 | 7                 | 230 / 2146           | 14265 / 335402       | 21                 | [1.8-2.4]                        | <0.000  | 6            | 0.62        |
|                                         | AA                 | 10                | 108 / 803            | 70 / 67              | 5.1                | [2.1-12.4]                       | <0.000  | 9            | <0.000      |
|                                         | SC                 | 7                 | 93 / 368             | 1236 / 342613        | 13                 | [6.2-26]                         | <0.000  | 8            | 0.24        |
|                                         | AA                 | 4                 | 2126 / 1038          | 82 / 1872            | 11.8               | [9.2-15]                         | <0.000  | 6            | <0.000      |
|                                         | SCD                | 9                 | 460 / 3836           | 3836 / 342613        | 13                 | [6.2-26]                         | <0.000  | 3            | 0.8         |
|                                         | SCD                | 3                 | 161 / 308            | 75 / 1764            | 4.3                | [0.6-29.9]                       | 0.13    | 2            | <0.000      |
|                                         | AA                 | 2                 | 147 / 287            | 246 / 10286          | 58                 | [10-319]                         | <0.000  | 3            | <0.000      |
|                                         | SC                 | 8                 | 225 / 432            | 2319 / 423           | 2.4                | [1-7.3-4]                        | <0.000  | 7            | 0.06        |
| Painful crisis                         | AA                 | 3                 | 115 / 460            | 0 / 880              | 117.1              | [23.4-586]                       | <0.000  | 2            | 0.7         |
|                                         | SC                 | 3                 | 170 / 438            | 78 / 328             | 1.5                | [0.8-2.8]                        | 0.1     | 4            | <0.000      |
| Acute Chest Syndrome                   | AA                 | 4                 | 60 / 510             | 0 / 930              | 33                 | [7.9-137.5]                      | <0.000  | 3            | 0.4         |
|                                         | SC                 | 4                 | 27 / 242             | 22 / 300             | 1.6                | [0.9-2.8]                        | 0.1     | 3            | 0.9         |

**UTI:** Urinary tract infection, **BT:** Blood transfusion

Mixed-effects analysis: The mixed-effects analysis demonstrated that the year of publication, quality of study reporting, and GNI comprised the heterogeneity factors in comparing HbSS and HbAA groups for the outcomes of prematurity, PIH, LSCS, UTI, BT, in comparing SCD vs. HbAA for the cesarean section, live births, LBW, IUFD, BT, comparing SCD vs. SCT groups for the cesarean section, in (SCT vs HbAA) for (LSCS), and comparing HbSS vs HbSC groups for LBW. Also, the year of publication, and quality of reporting were found as the
Table 5: Mixed-effects analysis by (year of publication, quality of reporting, and country gross national income-GNI).

| Variable          | Subgroup          | Quality of study reporting | Odds ratios                          | Country gross national income (GNI) |
|-------------------|-------------------|-----------------------------|--------------------------------------|------------------------------------|
|                   |                   | High | Moderate | High | Upper-middle | Lower-middle | Low | P         |
| PROM              | SCD-AA            | -    | -        | <0.0001 | 0.8[0.6-1] | -            | 1.1[0.26] | - | 0.11      |
| PPH               | SCD-AA            | 1.5[1.2-1.9] | 10.5[1-104] | <0.0001 | 1.5[1.2-2] | -            | 4.8[0.8-28] | - | <0.0001 |
|                   | SCD-AA            | 0.9[0.2-3.1] | 5.7[0.36-88] | 0.69 | -            | -            | -            | - | -         |
| Prematurity       | SCD-AA            | 1.1[0.6-1.8] | 6.9[0.7-67] | 0.37 | 1[0.8-1.3] | -            | 4.5[0.7-26] | - | 0.54      |
|                   | SCD-AA            | 3.7[1.8-7] | 6[2.3-16] | <0.0001 | 4.8[3.5-6.6] | 4.5[1.3-15.7] | 5.5[1.7-18] | - | <0.0001 |
| PIH               | SCD-AA            | 1[0.8-1.5] | 20[5.7-75] | 0.05 | 1.3[1.09-1.5] | 4.2[0.2-83] | - | -         |
|                   | SCD-AA            | 5.2[2.9-9.3] | 5.8[0.3-110] | <0.0001 | 3.5[2-5.9] | 1.2[0.4-3.6] | 18[2-111] | - | <0.0001 |
| Eclampsia         | SCD-AA            | 4.1[1.6-10] | 1.4[0.9-2.2] | 0.004 | 3.3[1-10] | -            | 2.2[1-4.6] | - | 0.004     |
| Cesarean section  | SCD-AA            | 3.5[1.7-6.8] | 1.8[1.3-2.4] | <0.0001 | 1.6[1.3-2.1] | 3.6[2.3-5.9] | 2.8[1.3-5.9] | - | <0.0001 |
|                   | SCD-SCT           | 3.5[2.1-5.9] | 1.1[0.5-2.1] | <0.0001 | 0.7[0.3-1.6] | 1.9[0.75-5.1] | 3.4[0.3-1.6] | - | <0.0001 |
| LSCS              | SCD-AA            | 1.9[0.56-9] | 25[10.3-63] | <0.0001 | 8.6[0.9-76] | -            | 8.2[0.5-125] | - | 0.01      |
|                   | SCD-AA            | 27[1.2-572] | 6[0.7-50] | 0.009 | 5[2-11] | 1.1[0.6-2] | 39[18-81] | - | <0.0001 |
| Live births       | SCD-AA            | 0.08[0.03-0.2] | 0.1[0.06-0.3] | <0.0001 | 0.1[0.06-0.3] | 0.3[0.2-0.5] | 0.08[0.04-0.1] | - | <0.0001 |
| LBW               | SCD-AA            | 4.7[1-22] | 2.9[2.1-3.9] | <0.0001 | 5[0.9-33] | -            | 3[2-3.8] | - | <0.0001 |
|                   | SCD-AA            | 11.6[0.05-2196] | 4.6[0.63-34] | 0.08 | -            | -            | -            | - | -         |
|                   | SCD-AA            | 69[38-125] | 17[0.95-319] | <0.0001 | 96[38-125] | -            | 17[0.9-319] | - | <0.0001 |
|                   | SCD-SC            | 2.2[1.3-8.3] | 0.9[0.04-18] | 0.02 | 3.8[2.2-6.8] | -            | 0.1[0.08-0.45] | 2[1.1-3.7] | 0.005    |
| IUGR              | SCD-SCT           | 0.5[0.1-2.2] | 4[1.7-9.4] | 0.02 | 3[0.6-16] | -            | 1.1[0.2-6] | - | 0.2       |
|                   | SCD-AA            | 2[0.6-6.5] | 19[6.2-62] | <0.0001 | -            | -            | -            | - | -         |
| Perinatal mortality | SCD-AA          | -    | -        | -    | 5.3[0.4-60] | -            | 12[0.4-258] | - | 0.04      |
| IUFD              | SCD-AA            | 16[0.55-496] | 6.5[2.6-16] | <0.0001 | 281[209-376] | -            | 5.2[2.2-12] | - | <0.0001 |
| Severe Anemia     | SCD-SCT           | 0.1[0.01-0.9] | 3.5[0.5-22] | - | 0.77 | -            | -            | - | -         |
| UTI               | SCD-AA            | 3.4[2.2-5] | 10[1.9-56] | <0.0001 | 3.9[2-7] | -            | 6.7[1.8-25] | - | <0.0001 |
| BT                | SCD-AA            | 26[10-67] | 28[3-236] | <0.0001 | 45[10-203] | -            | 15[2.3-104] | - | <0.0001 |
|                   | SCD-SC            | 0.1[1.1-1.9] | 11[1.9-62] | 0.002 | 3.2[0.8-36] | -            | 5[0.3-68] | - | 0.12      |
| Painful crisis    | SCD-SC            | 38[14-101] | 235[86-639] | <0.0001 | 236[32-1722] | -            | 82[12.6-545] | - | <0.0001 |

PROM: Premature rupture of membranes, PPH: Postpartum hemorrhage, PIH: Pregnancy-induced hypertension, LSCS: Lower segment caesarean section, LBW: Low birth weight, IUGR: Intrauterine growth restriction, IUFD: Intra-uterine fetal death, UTI: Urinary tract infection, BT: Blood transfusion
heterogeneity factors in comparing SCD vs. HbAA for PPH. The quality of study reporting, and GNI were found as the heterogeneity factors in the comparison of HbSS vs. HbAA for LBV. The year of publication of the study and GNI were found as the heterogeneity factors in comparing HbSS vs. HbAA for perinatal mortality. Also the quality of reporting the results reporting) was a heterogeneity factor for the outcome (IUGR) in comparing SCT vs. HbAA and SCD-SCT, and also for the BT outcome in comparing SCT vs. HbAA. The detailed effect of these factors on the study results is reported in Table 5.

**Publication bias assessment:** In the present study, publication bias was estimated via the Egger test and the results are shown in Table 3-5. The graphical funnel plots were symmetrical in most zones and did not reveal any bias.

**DISCUSSION**

This systematic review and meta-analysis showed that pregnancy in SCD increased the risk of adverse outcomes for the mother (including PPH, prematurity, PIH, pre-eclampsia, eclampsia, cesarean section, LSCS, maternal death), and for the fetus (live births, LBW, IUGR, APGAR score at 5 min <7, stillbirth, neonatal death, perinatal mortality, AFD, IUFD) and morbidity among patients with the SCD (severe anemia, UTI, BT, painful crisis, acute chest syndrome, VOC). The results of the present study are consistent with the results of a meta-analysis conducted by Boafor et al. (2016). They reported that SCD was associated with IUGR (pooled OR 2.79, 95% CI: 1.85–4.21), perinatal mortality (pooled OR 3.76, 95% CI: 2.34–6.06), and LBW (pooled OR 2.00, 95% CI: 1.42–2.83). SCD was also associated with an increased risk of pre-eclampsia (pooled OR 2.05, 95% CI: 1.47–2.85), maternal mortality (pooled OR 10.91, 95% CI: 1.83–65.11, P = 0.009), and eclampsia (pooled OR 3.02, 95% CI: 1.20–7.58) (4). The results of the present study are consistent with a meta-analysis by Oteng-Ntim et al. (2015). As these researchers reported, 21 studies (including 26,349 women with SCD and 2615746 women without SCD) were selected. Pregnancies in women with HbSS vs. HbAA were at an increased risk of maternal mortality (relative risk [RR], 5.98; 95% confidence interval [CI], 1.94 18.44), pre-eclampsia (RR, 2.43; 95% CI: 1.75-3.39), stillbirth (RR, 3.94; 95% CI: 2.60-5.96), preterm labor (RR, 2.21; 95% CI: 1.47-3.31), and small for gestational age infants (RR, 3.72; 95% CI: 2.32-5.98). A meta-regression revealed that in HbSS vs. HbSC, low gross national income, and high study quality were related to the increased RRs (6). In the present study, the mixed-effects analysis showed that in studies in lower-middle income group, the HbSS vs. HbAA genotype was associated with increased RRs in prematurity, PIH, LSCS, perinatal mortality, and UTI, and that HbAS vs. HbAA was associated with increased RRs in PIH and that SCD vs. HbAA was associated with increased RRs in PPH. Also, SCD vs. SCT genotype was associated with increased RRs in the cesarean section. In the studies in high income group, the HbSS vs. HbAA genotype and SCD vs. HbAA were associated with increased RRs in LBW, BT and HbSS vs. HbSC was associated with increased RRs in LBW. Despite the current developments in health care, especially in taking care of pregnant women over the past 4 decades, the maternal and fetal morbidity and mortality rate is high. The therapeutic interventions to improve pregnancy complications and morbidity comorbidity and the increased risk of adverse fetomaternal outcomes [6]. Contrary to the existing developments in obstetrics, and neonatal medicine, there is still a close association between pregnancy complications and morbidity comorbidity and the increased risk of adverse fetomaternal outcomes [6].
HbSC genotype was associated with increased RRs in LBW. The HbSS vs. HbAA genotype was associated with increased RRs in BT and the HbAS vs. HbAA genotype. Totally, the adverse outcomes in pregnancy were worse and more prevalent in pregnant women with SCD vs. those without SCD. This study reports that pregnancy complications are more frequent in HbSS than other genotypes. These findings are matched with the reports of several studies (6, 15, 57, 58). The outcomes of pregnancy in the HbSS genotype were worse than HbAA and HbAS. Also, fetomaternal outcomes were worse in HbAS when compared with HbAA. The decreased risk of adverse pregnancy outcome in women with HbSC is matched with the manner of the HbSC genotype. This genotype is frequently benign and may not be recognized until later in adult life (15). The results of a study in Brazil indicated that in women with SCD, the HbSS genotype was associated with a higher frequency of blood transfusion. Also, Sβ-thalassemia was associated with a higher frequency of postpartum adverse events (59). In this study, HbSC women had better pregnancy outcomes. However, the incidence of sickle cell-related complications did not differ between women with the HbSS and HbSC genotype. Therefore, it is not yet possible to predict SC patients who may develop severe complications in pregnancy and it is an acceptable practice to assess all pregnancies in SCD expecting a baby in the hospital. However, Malinowski et al. suggested that early identification of women with SCD at high risk of maternal and fetal pregnancy adverse outcomes can be predicted using routine clinical and laboratory data (60). There are some limitations of this systematic review which should be noted. First, this systematic review was not registered on prospective registration systems for systematic reviews. Prospective registration could improve the quality of a systematic review and increase confidence in the findings. However our results were reported according PRISMA statement in order to minimize possible bias. Second, we did not searched the grey literatures and may could not identify any unpublished research. Like with any systematic review, there is always the risk of publication bias as studies with negative results are usually not published.

According to the results of this meta-analysis, pregnancy in the SCD is associated with an increased risk of maternal outcomes, fetal outcomes, and morbidity among patients with the SCD. This condition requires careful multidisciplinary management and cautious caring so as to decrease maternal and fetal morbidity and mortality. Therefore, accurate and timely follow-up and monitoring of these pregnancies with a multidisciplinary team comprised of a hematologist, an obstetrician, and a pediatrician is essential. Raising patients’ awareness and educating them through communication sessions and a timely screening of complications for women with the SCD are essential to decrease the associated risks.

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