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RESEARCH ARTICLE
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"COMPARISON OF FETOMATERNAL OUTCOME IN SICKLE CELL DISEASE WITH HBAA PATTERN DURING PREGNANCY"

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Abstract

Background: Sickle cell disease (SCD) is a hereditary hemoglobinopathy that causes various complications during pregnancy. Pregnant women with SCD face higher maternal and fetal risks compared to those with the normal hemoglobin (HbAA) genotype. These complications, including vaso-occlusive crises, anemia, preeclampsia, and fetal growth restrictions, contribute to poorer outcomes for both mother and child.

Objectives: This study aims to compare the fetomaternal outcomes between pregnant women with SCD and those with the HbAA pattern.

Methods: A comprehensive literature search was performed in databases such as PubMed, Scopus, and the Cochrane Library for articles published between 2013 and 2024. Inclusion criteria consisted of studies that evaluated study comparing fetomaternal outcomes in women with SCD versus HbAA during pregnancy were identified from databases including PubMed, Scopus, and Web of Science. Both randomized controlled trials and observational studies were included, and quality assessments were performed using the Cochrane Risk of Bias tool.

Results: A total of 10 studies met the inclusion criteria, involving 1,053 women (603 with SCD and 450 with HbAA). Women with SCD exhibited higher rates of severe anemia, preterm delivery, cesarean section, and complications such as vaso-occlusive crises and pregnancy-induced hypertension. Fetal outcomes in SCD pregnancies were marked by increased risks of intrauterine growth restriction (IUGR), low birth weight, and neonatal mortality, compared to the HbAA group, which generally had more favorable outcomes.

Conclusion: Pregnancies in women with SCD are associated with significantly higher maternal and fetal complications compared to those with the HbAA genotype. Multidisciplinary care is crucial to mitigate risks and improve outcomes for both mother and fetus.

Keywords: *sickle cell disease, HbAA pattern, fetomaternal outcome, pregnancy, maternal morbidity, fetal complications, preterm delivery, intrauterine growth restriction*

INTRODUCTION

Sickle cell disease (SCD) is a hereditary hemoglobinopathy characterized by the presence of hemoglobin S (HbS), which leads to the sickling of red blood cells, resulting in various clinical complications. [1] Pregnant women with SCD face increased risks of maternal and fetal morbidity and mortality compared to those with normal hemoglobin (HbAA). [2] This heightened risk is attributed to the pathophysiological changes associated with pregnancy, which can exacerbate the complications of SCD, including vaso-occlusive crises, acute chest syndrome, and increased susceptibility to infections. [3]

The physiological alterations during pregnancy, such as increased blood volume, hypercoagulability, and heightened metabolic demands, can significantly impact women with SCD. These changes may lead to a higher incidence of obstetric complications, including preeclampsia, gestational hypertension, and intrauterine growth restriction (IUGR). [4] Studies have demonstrated that pregnant women with HbSS genotype experience a greater frequency of adverse outcomes compared to those with HbAA genotype. For instance, the complication rates are markedly elevated in HbSS patients, with common issues including vaso-occlusive crises and urinary tract infections being reported at significantly higher rates than in their HbAA counterparts. [5]

Conversely, women with the HbAA genotype generally exhibit more favorable pregnancy outcomes. The absence of sickle-shaped cells allows for improved placental perfusion and oxygen delivery to the fetus, thereby reducing the risk of low birth weight and other adverse fetal outcomes [6] Research indicates that while maternal morbidity remains a concern for both groups, the overall fetomaternal outcomes can be comparable when adequate prenatal care is provided. [6]

The disparity in outcomes between these two groups underscores the necessity for specialized care protocols tailored to the unique challenges faced by pregnant women with SCD. Current management strategies emphasize the importance of multidisciplinary approaches that include obstetricians familiar with high-risk pregnancies and hematologists specializing in SCD. This collaborative care model is essential for optimizing maternal health and minimizing fetal risks during pregnancy. [7]

In addition, while sickle cell disease presents significant challenges during pregnancy that can adversely affect both maternal and fetal health, understanding the comparative outcomes between different hemoglobin genotypes is crucial. Enhanced prenatal care, early intervention strategies, and individualized management plans are vital for improving fetomaternal outcomes in this population. Continued research is needed to further elucidate the complexities of managing pregnancies in women with SCD and to develop effective interventions aimed at reducing morbidity and mortality rates associated with this condition.

MATERIALS AND METHODS

The protocol for this systematic review was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, including the PRISMA-P checklist for protocol reporting.

SEARCH STRATEGY

A comprehensive search strategy was implemented to identify relevant literature on the comparison of fetomaternal outcome in sickle cell disease with HBAA pattern during pregnancy.

The search encompassed multiple electronic databases, including MEDLINE via PubMed, Embase, Google Scholar, the Cochrane Library, Web of Science, Wiley Online Library, and Scopus. A combination of Medical Subject Headings (MeSH) terms and keywords was utilized, including

"fetomaternal outcome," "sickle cell disease," "HBAA pattern," "pregnancy outcomes," "fetal complications," "maternal morbidity," "perinatal mortality," and "sickle cell complications in pregnancy." The search was limited to studies published in English, and both randomized controlled trials and observational studies were considered for inclusion to ensure a comprehensive review of the available evidence.

Inclusion criteria

- RCTs (Randomized clinical trials)
- Articles that provide information on
- Clinical trials, full-text articles
- Articles written in the English language
- Studies focusing on pregnant women with sickle cell disease
- Studies on pregnant women with sickle cell disease
- Studies comparing HBAA pattern in sickle cell disease during pregnancy

Exclusion criteria

- Case reports, Case series
- Conference articles
- Incomplete texts or studies with insufficient data
- Duplicate articles that are excluded from the study
- Studies unrelated to pregnancy or sickle cell disease
- Articles before cade

DATA ANALYSIS:

Following the extraction of articles from various databases, the articles were organized in an excel sheet, where duplicates were systematically removed. Then each article's abstract was independently assessed and papers were selected according to the established protocol. The complete texts of the chosen papers were then thoroughly reviewed, resulting in the final selection of relevant research. Two reviewers independently performed full-text screening. For any differences of opinion that emerged during data extraction, consensus was reached between the two reviewers by discussion or consultation with a third reviewer.

QUALITY ASSESSMENT OF INCLUDED STUDY

The quality of individual studies was assessed using the Cochrane risk of bias tool in RevMan software for randomized controlled trials, with each study categorized as having a high, unclear, or low risk of bias across various domains such as selection bias (random sequence generation), performance bias (blinding of participants and personnel), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other potential sources of bias, ensuring a thorough and standardized evaluation of the methodological quality and potential for bias in the included studies.

STATISTICAL ANALYSIS:

In this review, a total of 10 studies were included, with data extraction piloted using Microsoft Office Excel 2013 and statistical analysis conducted through RevMan software version 5.4. The risk of bias for each study was evaluated separately by two review authors utilizing the Risk of Bias Tool for Randomized Controlled Trials, categorizing the studies as having a high risk (+), unclear risk (?), or low risk (-) based on various domains. This systematic approach ensured a thorough evaluation of the methodological quality of the included trials, allowing for a strong analysis of the overall findings and implications derived from the studies.

RESULTS

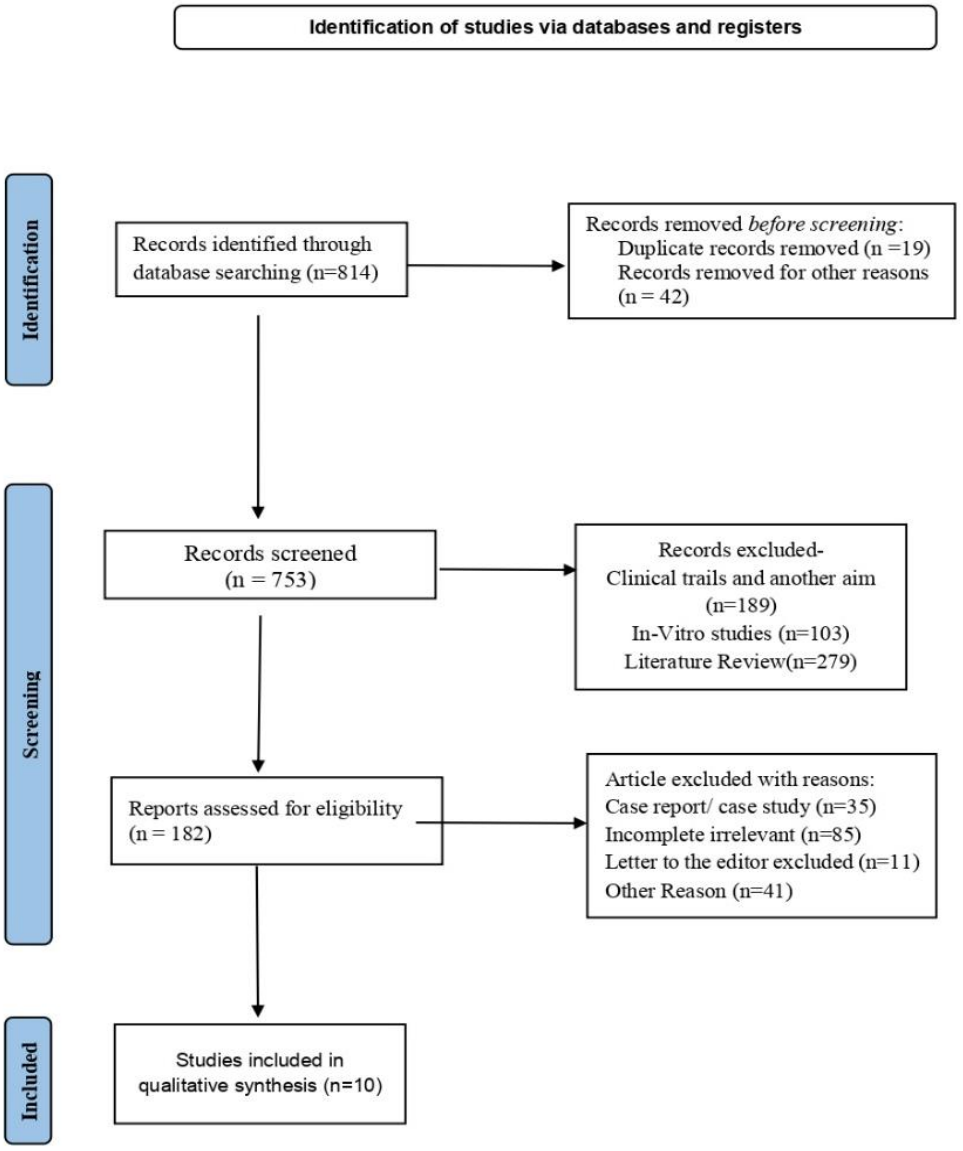

Figure 1. Illustrates the PRISMA flow diagram as well as the article's specified relevant database.

STUDY SELECTION:

In total, 814 articles were identified through database searches. Prior to screening, 19 duplicate records and 42 records for other unspecified reasons were excluded, resulting in 753 records for screening. From these, 189 records were excluded for not adhering to the inclusion criteria, and 103 reports proceeded to the eligibility assessment. Following this assessment, 279 reports were excluded as case reports or case studies, 182 as incomplete or irrelevant, 35 as letters to the editor, and 41 for various other reasons. After thorough screening and data analysis, a total of 10 studies were incorporated into the qualitative synthesis. This flowchart systematically depicts the reduction of the initial dataset to the final set of studies included in the analysis. The document screening flowchart is shown in Figure 1. Basic information included in the study is shown in **Table 1**

Sr. No	Author	Study design	Country	Sample Size (SCD/HBAA)	Maternal Outcome (SCD)	Maternal Outcome (HBAA)	Fetal Outcome (SCD)	Fetal Outcome (HBAA)	Key Findings
1	**Saif et al., 2024 [8]**	Retrospective case-control study	Oman	171/171	Higher risk of severe anemia, preterm delivery, NICU admissions	Lower risk of complications	Increased risk of IUGR, low birth weight, NICU admission	Lower risk of fetal complications	Women with SCD had significantly higher odds of adverse pregnancy, fetal, and neonatal outcomes. Vigilant management and improved antenatal care are crucial.
2	**Mian DB., et al 2023 [9]**	Retrospective case-control study	Ivory Coast	156/312	Severe anemia, preterm births, VOC, IUGR, IUFD, CS, acute chest syndrome	PIH, preeclampsia, eclampsia, PPH	Incidence of low birth weight, neonatal mortality, AFD, IUFD	Low rates of low birth weight, live birth, AFD, IUFD	HbAA is associated with better fetal and maternal outcomes compared to SCD, which is linked to severe anemia, low birth weight, and prematurity.
3	**Babah OA, et al 2019 [10]**	Prospective case-control study	Nigeria	50/50	Higher complication rate, including VOC, pregnancy-induced hypertension, UTI	Lower complication rate,	Low birth weight (<2.5 kg) was 38% in HbSS	Low birth weight (<2.5 kg) was 4% in HbAA	SCD presents elevated obstetric risks, but outcomes can be comparable to HbAA with appropriate care. No maternal deaths recorded in either group.

4	**Nwafor, J. et al 2019 [7]**	Retrospective case-control study	Nigeria	164/160	Higher CS rate, increased PIH and preeclampsia	Higher live birth rate, lower CS, PIH, and preeclampsia	Higher proportion of low birth weight (<2.5 kg)	Significantly higher birth weight	Maternal and fetal outcomes in SCD were generally worse than in HbAA. Maternal mortality rates were similar in both groups.
5	**Agbaje OA., et al 2019 [11]**	Cohort study	Nigeria	60/60	Higher rate of operative deliveries	Lower rate of operative deliveries.	Low birth weight (<2.5 kg). Higher IUFD, Higher IUGR,	Higher birth weight, lower IUFD, lower IUGR	Perinatal outcomes showed increased low-birth-weight babies in HbSS and higher pregnancy complications.
6	Warade S., et al 2019 [12]	Prospective study	India	54/54	Increased anemia, higher rates of UTIs and hypertensive disorders	Lower rates of complications	Higher incidence of pregnancy wastage and preterm deliveries	Fewer complications in HbAA pregnancies	Sickle cell hemoglobinopathies increase pregnancy complications. Vigilant management is required to improve outcomes.
7	**Gaddikeri A., et al 2017 [13]**	Hospital-based prospective study	India	54/54	Higher rates of anemia, preterm delivery, higher caesarean section rates.	Lower rates of complications	Low birth weight, higher IUFD	Low birth weight, higher IUFD, higher IUGR	Perinatal outcomes revealed increased low-birth-weight babies in HbSS and a higher incidence of pregnancy complications.

8	**Afolabi BB., et al 2016 [6]**	Prospective cross-sectional study	Nigeria	24/20	Earlier delivery, lower gestational age, reduced BMI,	Delayed delivery, longer gestation age, higher BMI	Low birth weight	Significantly higher birth weight	HbAA women had higher birth weights and delivered at a later gestational age compared to HbSS women. Birth weight was significantly correlated with plasma volume.
9	**Ugboma HA. et al [14]**	Retrospective case-control study	Nigeria	164/160	Higher CS rate	Higher live birth rate	Higher stillbirth rate in HbSS compared to HbSC (not significant)	Higher live birth rate in HbAA	Maternal mortality in SCD patients was similar to HbAA, but other outcomes were poorer in SCD pregnancies.
10	**Thame MM., et al (2013) [5]**	Prospective study	Jamaica	41/41	Lower diastolic BP, reduced hemoglobin, consistently lower weight, body fat, and lean body mass	Higher body measurements and BP	Lower birth weight, crown-heel length, head circumference (not significant after adjusting for gender and gestational age)	No significant growth restrictions or adverse effects after adjusting for gender and gestational age	Mothers with SS disease experienced lower birth weight and reduced crown–heel length in their babies, associated with bone pain crises during pregnancy, compared to AA genotype.

TABLE 1: Fetomaternal Outcomes in SCD vs. HBAA Pregnancies.

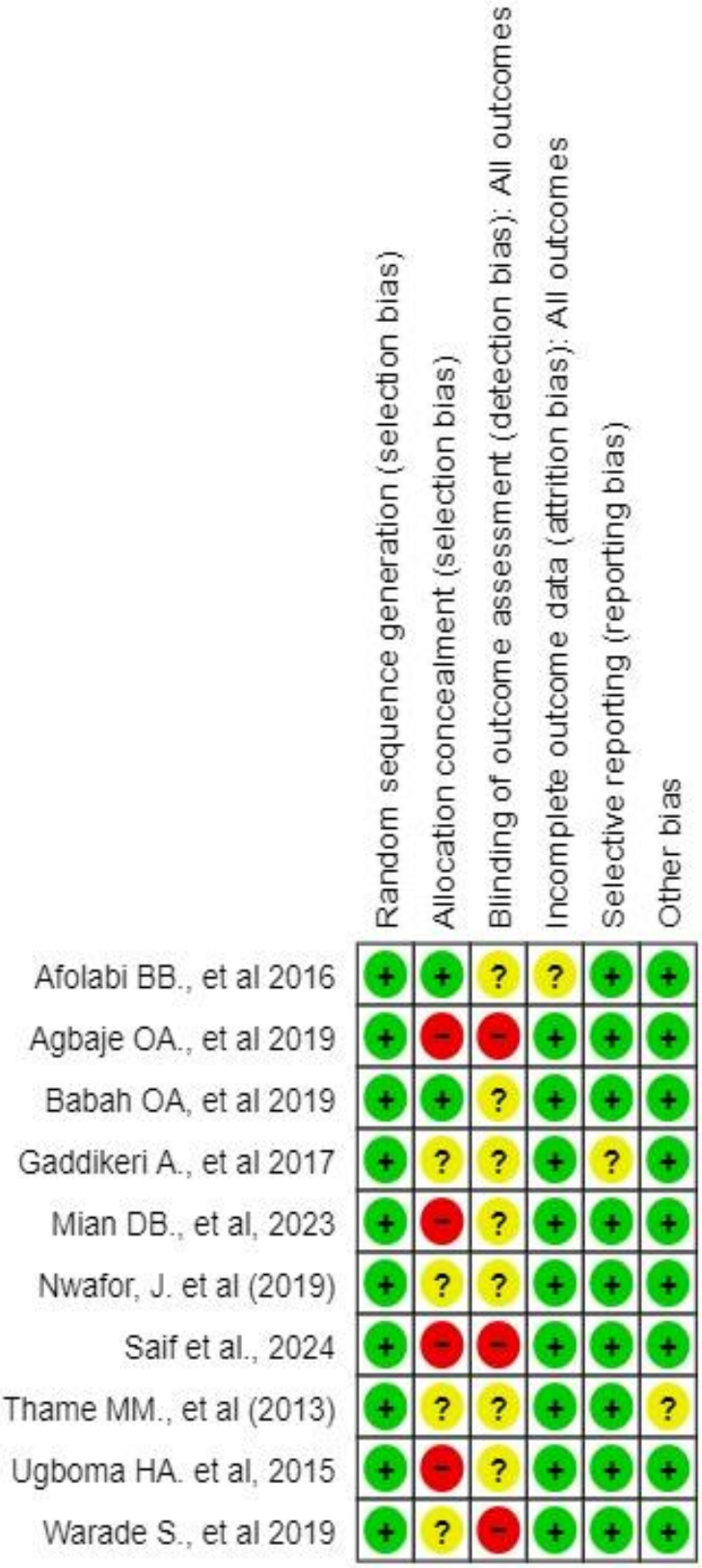

Fig 2: Summary of risk of bias: evaluation of each's study involved item's risk of bias

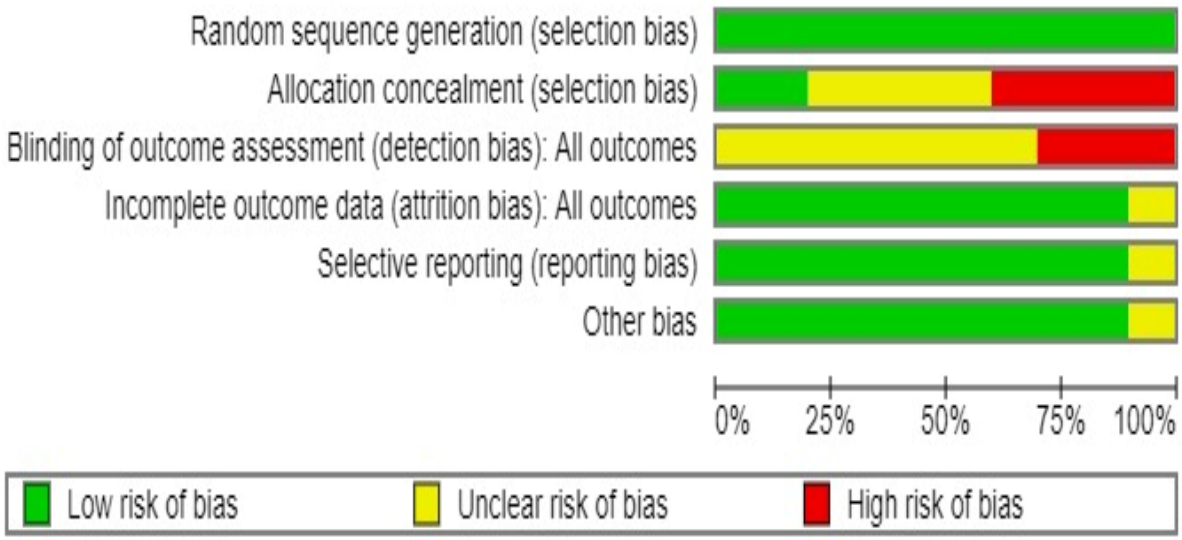

Figure 3: The author's evaluation of each risk of bias item represented as percentages through all involved articles in the risk of bias graph.

ELIGIBLE STUDIES CHARACTERISTICS:

In the present systematic review, we identified ten eligible studies that explored maternal and fetal outcomes in patients with Sickle Cell Disease (SCD) compared to those with Hemoglobin AA (HbAA). The review comprised a range of study designs, including 8 retrospective case-control studies and 2 prospective studies, conducted across diverse countries such as Nigeria, India, Jamaica, and Oman. The total sample size included 1,053 subjects, with 603 diagnosed with SCD and 450 with HbAA.

The findings consistently indicated that maternal outcomes were worse in SCD patients, with higher incidences of severe anemia, preterm delivery, and complications such as vaso-occlusive crises and pregnancy-induced hypertension. In contrast, maternal outcomes for HbAA patients were generally more favorable, showing lower complication rates and higher live birth rates. Fetal outcomes also demonstrated significant differences; SCD pregnancies were associated with an increased risk of intrauterine growth restriction (IUGR) and low birth weight, while HbAA pregnancies showed better fetal outcomes, including lower rates of neonatal mortality.

Table 1. summarizes the characteristics of the eligible studies, detailing the authors, study designs, countries, sample sizes, and maternal and fetal outcomes associated with SCD and HbAA. The systematic review utilized the Cochrane "Risk of Bias tool," designed specifically for both randomized and non-randomized studies, allowing for a comprehensive evaluation of bias across several domains, including patient selection, study conduct, and data interpretation:

- The method of randomization
- Deviations from intended interventions
- Missing outcome data
- Assessment of risk
- Bias in the selection of the reported result

The majority of articles received a low-risk rating (**65%)** based on the overall bias assessment for each selected work. A "low-risk" study utilized a reliable method to assign patients to different treatment courses, ensuring the reliability of the findings. An "unclear" study (**23.33%)** may have had some bias, but it was likely not sufficient to affect the accuracy of the results, possibly due to incomplete data. A "high-risk" study (**11.67%)** indicated a significant level of bias, potentially leading to erroneous findings, often due to knowledge gaps or reporting inconsistencies. [**Fig: 2, 3**]

DISCUSSION

This systematic review aggregates findings from multiple studies to elucidate the differences in maternal and fetal outcomes between women with sickle cell disease (SCD) and those with the normal hemoglobin genotype (HbAA). This systematic review highlights significant disparities in both maternal and fetal health outcomes, emphasizing the need for improved management strategies for pregnant women with SCD.

Maternal Outcome

The present, study show, that maternal outcomes in SCD were consistently poorer compared to those in the HbAA group.

Severe Anemia and Complications: Women with SCD exhibited a higher incidence of severe anemia, preterm deliveries, and complications such as vaso-occlusive crises (VOC), pregnancy-induced hypertension (PIH), and acute chest syndrome. For instance, **Saif et al.** (2024) [8] reported a significantly higher risk of severe anemia and NICU admissions among SCD patients compared to their HbAA counterparts. Similar, study highlighted that the physiological changes occurring during pregnancy, including increased metabolism, blood stasis, and coagulability, exacerbate SCD. Their study identified an increased risk of adverse effects for SCD mothers and neonates, with a particular focus on complications such as vaso-occlusive crises and acute chest syndrome. Additionally, result noted that the acidic conditions during pregnancy lower the oxygen affinity of abnormal hemoglobin (HbS), leading to its polymerization and the formation of sickled red blood cells (RBCs), which can obstruct blood flow and contribute to adverse fetal outcomes. [15]

Operative Deliveries: Increased rates of operative deliveries, including cesarean sections, were noted in SCD pregnancies. **Nwafor et al.** (2019) [7] indicated that women with SCD had higher cesarean section rates despite similar maternal mortality rates between the two groups.

Overall Complications: The cumulative evidence points towards an elevated risk of adverse maternal outcomes in SCD pregnancies, necessitating vigilant management and enhanced antenatal care to mitigate these risks.

Fetal Outcomes

Fetal outcomes also demonstrated significant differences between the two groups:

Low Birth Weight and IUGR: A recurrent theme across studies is the higher incidence of low birth weight and intrauterine growth restriction (IUGR) among infants born to mothers with SCD. For instance, **Babah et al.** (2019) [10] found that 38% of infants born to SCD mothers had low birth weight, compared to only 4% in the HbAA group.

Neonatal Mortality: The risk of neonatal complications, including mortality, was notably higher in the SCD cohort. **Mian et al.** (2024) [9] reported a higher incidence of neonatal mortality and adverse fetal outcomes such as intrauterine fetal demise (IUFD) among SCD pregnancies.

Birth Weight Correlation: **Thame et al.** (2013) [5] highlighted a significant correlation between maternal health indicators such as body mass index (BMI) and hemoglobin levels and fetal growth parameters. Mothers with SCD had lower birth weights for their infants, which could be attributed to compromised placental perfusion and nutritional deficiencies.

A similar systematic done by **Aghamolaei T et al [2]** consistently show that pregnant women with Sickle Cell Disease (SCD) have significantly worse fetal outcomes compared to those with the HbAA genotype. This includes a statistically significant decrease in live births and increased risks of low birth weight (LBW), intrauterine growth restriction (IUGR), low Apgar scores, stillbirth, neonatal death, perinatal mortality, and adverse fetal development (AFD). These risks are especially pronounced in women with the HbSS genotype compared to HbAA.

The comparison between HbAS and HbAA genotypes revealed increased relative risks (RRs) for lower segment cesarean section (LSCS).The Sickle Cell Disease (SCD) genotype was associated with higher RRs for complications such as eclampsia, intrauterine fetal death (IUFD), and bleeding disorders (BT) when compared to HbAA. Additionally, the HbSS genotype showed increased RRs for low birth weight (LBW) in comparison to the HbSC genotype. Furthermore, the HbSS genotype

demonstrated elevated RRs for bleeding disorders when compared to the HbAA genotype. Overall, adverse pregnancy outcomes were significantly worse and more prevalent among pregnant women with SCD compared to those without. [16, 17, 18] This study indicates that pregnancy complications are more frequent in individuals with the HbSS genotype than in other genotypes. These findings are consistent with the results reported in several other studies.

Key Findings and Implications

Need for Enhanced Antenatal Care: The findings advocate for tailored antenatal care protocols for women with SCD to monitor and manage complications proactively. This includes regular screening for anemia and hypertension, as well as nutritional support.

Interdisciplinary Management Approach: Collaboration among obstetricians, hematologists, and pediatricians is essential to optimize both maternal and fetal outcomes.

Further Research Directions: There is a pressing need for longitudinal studies focusing on long-term maternal and fetal health outcomes post-delivery in women with SCD, as well as interventions aimed at improving pregnancy outcomes. However, **Malinowski et al.** (2021) [21] suggested that women with Sickle Cell Disease (SCD) at high risk for adverse maternal and fetal outcomes during pregnancy can be effectively identified through the analysis of routine clinical and laboratory data.

Moreover, this systematic review highlights the stark contrast in maternal and fetal outcomes between women with sickle cell disease and those with the HbAA genotype during pregnancy. The evidence calls for enhanced clinical vigilance and tailored management strategies to improve health outcomes for this vulnerable population.

CONCLUSION

The comparison of fetomaternal outcomes between sickle cell disease and the normal hemoglobin genotype reveals significant disparities in both maternal and fetal health risks during pregnancy. Women with SCD experience elevated risks of complications such as severe anemia, preterm deliveries, and adverse neonatal outcomes like low birth weight and IUGR. However, proactive management strategies can help mitigate these risks, underscoring the importance of comprehensive prenatal care tailored to the needs of women with sickle cell disease.

ABBREVIATIONS:

- SCD: Sickle Cell Disease
- HbSS: Hemoglobin SS
- HbAA: Hemoglobin AA
- VOC: Vaso-Occlusive Crisis
- IUGR: Intrauterine Growth Retardation
- IUFD: Intrauterine Fetal Death
- CS: Caesarean Section
- PIH: Pregnancy-Induced Hypertension
- PPH: Postpartum Hemorrhage
- AFD: Abnormal Fetal Development
- UTI: Urinary Tract Infection
- NICU: Neonatal Intensive Care Unit
- BP: Blood Pressure

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