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Sickle Cell Disease: Can genetic variability influence pregnancy outcomes?

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ABSTRACT

Pregnancy in Sickle Cell Disease (SCD), a severe hereditary genetic condition, highly prevalent in Sub-Saharan African countries, is associated with increased risk of complications and severe outcomes in pregnancy, like intrauterine growth restriction, low birth weight, premature birth, miscarriage, stillbirth, pre-eclampsia, and maternal mortality. Several factors have been identified as associated with the heterogeneity of SCD phenotypes, namely the hemoglobin subunit beta (HBB) haplotype and −3.7 kb α-thalassemia deletion.

Objective: This study aimed to identify pregnancy complications and severe outcomes, and their association with genetic variability in women with SCD.

Methods: In a cohort of 162 pregnant women followed at Maternidade Lucrécia Paim, Luanda, Angola, we collected clinical, hematological, biochemical, and genetic data (Sickle Cell Disease genotype, HBB haplotype, and −3.7 kb α-thalassemia).

Findings: The Central African Republic (CAR) haplotype was the most prevalent, being 87% of women homozygous. For the −3.7 kb α-gene deletion 11.7% of women were homozygous, and 36.4% were heterozygous. In this cohort, CAR/CAR women had over 9 times higher odds of having a premature birth, and homozygous women for the −3.7 kb α-thalassemia had over four times higher odds of having a livebirth than the other genotypes. Over 50% of babies were born with low birth weight, and 52,7% were considered premature. Severe maternal complications were registered in 68% of current pregnancies.

Conclusion: These findings highlight the high burden of adverse outcomes in SCD pregnancy and the need for individualized and closer healthcare, especially in low and middle-income countries.

1. Introduction

Sickle Cell Disease (SCD) is a group of hematological hereditary disorders affecting more than 7 million people worldwide. Each year, an estimated half a million babies are born with this severe disease, with approximately ¾ of cases occurring in Sub-Saharan Africa (SSA) [1]. A single-nucleotide substitution in the hemoglobin subunit beta (HBB) gene, which codes for the beta-globin chain, results in the production of an anomalous hemoglobin, hemoglobin S, that tends to polymerize under low oxygen pressure, leading to erythrocyte sickling and making patients more susceptible to vaso-occlusive events, oxidative stress, hemolysis, and inflammation [2,3].

In terms of severity and lifespan, SCD is considered a heterogeneous disease. Previous findings have shown that the persistence of high values of fetal hemoglobin (HbF) positively impacts the clinical presentation of this disease. The study of several polymorphisms in the β-globin gene cluster led to the identification of five distinct HBB haplotypes, which, based on the geographical distribution, were identified as Arab-Indian

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(AI), Senegal (SEN), Cameroon (CAM), Benin (BEN), and Central African Republic/Bantu (CAR) [4]. The CAR haplotype, considered the most severe due to its association with lower HbF levels, is the most predominant in Angola, where the limited available neonatal screening data indicate a disease prevalence that can exceed 3% and a carrier frequency of the S allele higher than 20% [5–9].

The coinherence of α-thalassemia deletion has also been correlated with phenotypic diversity of SCD patients, with the −3.7 kb deletion being the most common alpha-deletion among individuals of African descent [10,11]. The reduction in intracellular hemoglobin and consequent decrease in hemoglobin polymerization is associated with fewer hemolytic complications. However, the increment of blood viscosity associated with α-thalassemia might lead to an increase in other common manifestations of the disease, such as painful crises, acute chest syndrome, and osteonecrosis [12].

Even though in low and middle-income countries (LMIC), early diagnosis remains generally unavailable and the under-five mortality rate is still very high, an increasing number of women are now surviving to childbearing age [1,13]. Pregnancy brings metabolic changes in the mother's organism, with the purpose of creating the perfect environment for the development of the fetus. These changes will cause an exacerbation of the patient's symptoms and worsen their anemia. In fact, pregnancy in SCD is associated with increased risk of complications and severe outcomes, not only for the mother, with higher risk of pre-eclampsia, eclampsia and maternal mortality, but also for the fetus, with higher risk of intrauterine growth restriction, low birth weight, miscarriage and perinatal death [14,15].

In the present study, we intended to identify severe outcomes and complications in a cohort of SCD pregnant patients in Angola, in a two-year period, and study their possible associations with genetic variability, specifically HBB haplotypes and − 3.7 kb α-thalassemia deletion.

2. Patients, materials and methods

2.1. Study population

The sample population consisted of 162 pregnant SCD patients, followed at Maternidade Lucrécia Paim (MLP), Luanda, Angola. Eligibility criteria included not being treated with hydroxyurea for at least 3 months. A complete anamnesis questionnaire was performed in the first medical appointment. Data collected included sociodemographic characteristics, previous disease manifestations, previous pregnancies, and current symptoms. In follow-up appointments, the clinician collected clinical data and included the registry of the events between consultations, namely hospitalizations, transfusions, and pain crises. At delivery, data collected included gestational age, type of delivery (c-section or eutocic) and birth weight.

2.2. Assessment of hematological and biochemical parameters

A blood sample was collected in every consultation for hematological and biochemical analysis. The hematological parameters measured comprised complete cell blood count, total hemoglobin (HGB), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) using the XT-2000i Hematology Analyzer (Sysmex Corporation, Kobe, Japan). Biochemical blood tests included Lactate dehydrogenase (LDH), total and direct bilirubin, blood glucose, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), urea, and creatinine, using Mindray BA-88A (Mindray, Shenzhen, China) and Cobas C111 (Roche Diagnostics, Rotkreuz, Switzerland).

2.3. Genetic analysis

Genomic DNA was extracted from blood samples with the QIAamp DNA Blood Mini Kit (Qiagen GmbH, Hilden, Germany) and its purity and quantification assessed with a NanoDrop™spectrometer (ThermoFisher Scientific Inc., Waltham, MA, USA). The patient's genotype was confirmed by PCR-RFLP. For one heterozygous patient, the HBB gene was sequenced by Sanger [5].

To determine HBB haplotype, 5 SNPs were studied: rs3834466 (HBE), rs28440105 (HBG1), rs2070972 (HBG2) by PCR-RFLP [16,17] and rs10128556 (HBBP1) and rs968857 (HBD) by real-time PCR using the TaqMan™ Assays (ID: C__9599121_10 and C_30114237_20; Thermo Fisher Scientific, Waltham, MA, EUA). GAP-PCR was performed to assess the −3.7 kb α-thalassemia deletion [18].

2.4. Statistical analysis

Statistical analysis was performed using Jamovi, version 2.6 [19]. Normal distribution of all continuous variables was evaluated using the Shapiro-Wilk test. For independent samples with normal distribution and homogeneous variances, Student's *t*-test was used. For heterogeneous variances, the Welch's t-test, and when these assumptions were violated, the Mann-Whitney test. Values for continuous variables are presented as mean ± standard deviation. Categorical variables were analyzed using the chi-squared test. Binary logistic regression was used to calculate the odds ratio (OR), considering two-tailed *p*-values and a 95% confidence interval. Hardy-Weinberg equilibrium was determined using GENEPOP 4.7.5. [20]. Values were considered statistically significant if p-value≤0,05.

3. Results

A total of 162 pregnant women with SCD were enrolled in this study, of which 15 were recruited during the 1st trimester, 138 during the 2nd, and 16 only in the 3rd (Fig. 1). The loss to follow-up marked this study and compromised the assessment of events throughout the pregnancies, namely the number of vaso-occlusive crisis, transfusions, and hospitalizations.

Ages ranged from 16 to 46 years (25.92 ± 5.75). The SS genotype was confirmed for 161 women, and one patient was diagnosed with Sickle-β^0thalassemia (SNP rs33945777).

Past clinical history analysis shows that the mean age at diagnosis was 5.9 months (SD 6.6), 94.9% of the time due to disease complications. The first manifestations of SCD included painful crisis (86.7%), severe anemia (38.1%), and dactylitis (27.6%). More than 90% of patients have already been hospitalized at least once, with pain crisis being the primary reason mentioned (81.1%). A total of 79.8% of patients reported having received at least one blood transfusion during their lifetime.

At the time of recruitment, 23.4% of pregnant women mentioned being in pain crisis, 13.5% reported weakness, 58.8% presented light jaundice, 15.7% moderate to severe jaundice, and 9.5% palpable liver.

Hematological and biochemical profiles of patients (20 to 28 weeks of gestational age) are presented in Table 1. Severe anemia was identified in 39.3% of women, and 59.8% had moderate anemia [21].

3.1. Fetal and maternal pregnancy outcomes

Concerning previous pregnancies, 53.9% of patients reported prior pregnancies. Considering all not voluntarily terminated previous pregnancies, 19.6% resulted in stillbirth (baby's death after 28 weeks of pregnancy, before or during childbirth [22]) and 22.7% in miscarriages (death before 28 weeks of gestation [23]), yielding a livebirth rate of 57.7%. C-section rate was 37.6%.

During the study, a considerable proportion of patients were lost to follow-up (Fig. 1). Only fifty women had their final consultation at MLP and 11 stillbirths (22.0%) were registered. For livebirths (78%), the mean birth weight was 2.49 ± 0.46, and 52,7% were considered premature (WHO's definition: born before 37 weeks of gestation [24]). C-sections outnumbered eutocic births, with 88.1% of deliveries

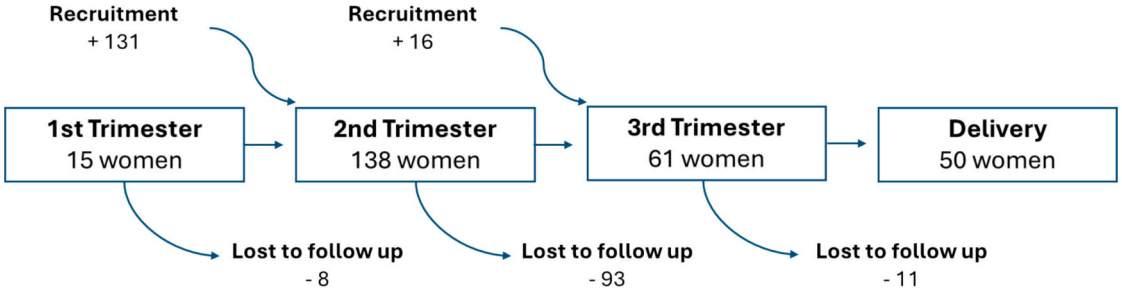

Fig. 1. Flow diagram of patient inclusion and loss to follow-up.

Table 1
Hematological and biochemical parameters of the SCD pregnant women (20th to 28th week gestational age).

	N	Mean ± SD
RBC (10^{12}/L)	122	2.56 ± 0.59
HGB (g/dL)	122	7.20 ± 1.08
HCT (%)	122	21.06 ± 3.44
MCV (fL)	122	84.55 ± 13.36
MCH (pg)	122	28.80 ± 4.37
MCHC (g/dL)	122	34.29 ± 2.10
WBC (10^9/L)	120	11.64 ± 8.38
PLT (10^9/L)	121	300.00 ± 150.34
GLU (mg/dL)	103	54.83 ± 23.50
TBIL (mg/dL)	109	1.47 ± 1.18
DBIL (mg/dL)	89	0.52 ± 0.44
ALT (U/L)	117	18.45 ± 27.06
AST (U/L)	117	47.87 ± 67.52
CREAT (mg/dL)	110	0.44 ± 0.17
UREA (mg/dL)	112	11.55 ± 6.02
LDH (U/L)	95	702.90 ± 473.88

(RBC – erythrocytes, HGB – total hemoglobin, HCT – hematocrit, MCV – Mean corpuscular volume, MCH – mean corpuscular hemoglobin, MCHC – mean corpuscular hemoglobin concentration, WBC – white blood cell count, PLT – platelets, GLU – glucose, TBIL – total bilirubin, DBIL – direct bilirubin, ALT - Alanine Aminotransferase, AST – aspartate aminotransferase, CREAT – creatinine, LDH - Lactate Dehydrogenase, N – number of individuals, SD – standard deviation)

registered. Severe maternal complications were registered in 34 of these 50 deliveries: 1 maternal death, 1 stroke, 2 acute thoracic syndrome, 4 sepsis, 2 post-partum bleeding, 11 cases of pre-eclampsia, 10 severe anemia, 11 vaso-occlusive crisis, and 7 oligohydramnios.

3.2. Alpha-thalassemia

In this cohort, 11.7% ($n = 19$) of women were homozygous for the −3.7 kb α-thalassemia deletion and 36.4% ($n = 59$) were heterozygous. Hardy-Weinberg equilibrium was evaluated, and no significant deviation was detected ($p = 0.0939$).

Hematological and biochemical analysis showed significant differences between the groups (Table 2). Homozygous for the deletion presented lower white blood cell (WBC) count, MCV, MCH, MCHC, and bilirubins than other genotypes. Also, they presented higher erythrocyte count (RBC) and hematocrit (HCT). There were no differences between previous hospitalizations and transfusions between genotypes (p-value = 0.946 and 0.139, respectively). At the time of recruitment, 35.7% of homozygous individuals for the deletion reported experiencing a pain crisis (heterozygous 23.8% and homozygous with no deletion 19.6%, p-value 0.450). Regarding complaints of weakness, homozygous for the deletion totalize 7.7%, vs 16.7% for heterozygous and 12.2.% for the homozygous with no deletion (p-value = 0.669). In homozygous individuals for the deletion, light jaundice was present in 50%, and no cases of moderate to severe jaundice were identified (p-value = 0.020). For heterozygous and homozygous individuals with no deletion, light jaundice was identified in 65.9% and 55.1% of cases, and moderate to severe jaundice in 7.3% and 26.5%, respectively.

In what concerns fetal outcomes, in previous pregnancies, homozygous individuals presented a higher rate of livebirths (82.4%) than other genotypes (52.4%) (p-value = 0.046, OR 4.222 [1.126;15.833]).

3.3. HBB haplotypes

Regarding HBB haplotypes, 87% of women had the CAR/CAR haplotype (Table 3), and 11.7% were heterozygous for the CAR allele. The hematological and biochemical data showed significant differences between CAR/CAR women and other genotypes (Table 4). CAR/CAR patients presented with lower RBC, hemoglobin, and HCT, along with higher LDH. Considering previous hospitalizations and transfusions, there were no significant differences between CAR/CAR women and other genotypes. At the time of recruitment, 24.5% of CAR/CAR women complained of being in pain crisis, and 14.3% felt weakness, versus 15.4% and 7.7% of other genotypes, respectively. Light jaundice was identified in 58.4% of CAR/CAR women, and moderate to severe in 16.8%, against 61.5% and 7.7% of other genotypes.

Regarding fetal outcomes, in previous pregnancies, the perinatal survival rate was lower in CAR/CAR patients (56.5% vs 66.7%, p-value = 0.721), and the rate of miscarriages was higher (24.7% vs 8.3%, p-value = 0.287). In current pregnancies, 61.3% of CAR/CAR women had their babies before 37 weeks of gestation, which is considered a premature birth [25], and the other genotypes 14.3% (p-value = 0.049, OR 9.5 [1.014–88.966]).

4. Discussion

SCD is highly prevalent in Angola, and since an increasing number of women are reaching childbearing age, it is crucial to reflect on the complications associated with pregnancy in these patients, and to explore strategies for preventing or mitigating its consequences, for both mother and fetus.

In this Angolan cohort of SCD pregnant women, 39.3% of women presented severe anemia (hemoglobin below <7.0 g/dL), and 59.8% had moderate anemia (hemoglobin <9.5 g/L). [21] This undermines the oxygen delivery to the tissues, namely the placenta, which will lead to several of the complications associated with SCD pregnancy.

5. Maternal pregnancy outcomes

Previous studies already demonstrated that SCD pregnant women are more prone to the development of pre-eclampsia and eclampsia and have a higher risk of maternal death [14].

In this Angolan cohort pre-eclampsia was identified in 11 of 50 women (22%). A meta-analysis from 2016 showed that pregnant women with SCD had a 2.05 times higher risk of pre-eclampsia than women without the condition, but if limiting the data only to LMIC, the OR rises to 2.41 [14]. In France, a recent nationwide study reported an incidence of 9.6% in SCD women vs 1.7% in women without the condition [26].

Table 2
Hematological and biochemical parameters of the SCD pregnant women, grouped by −3.7 kb α-thalassemia deletion (20th to 28th week gestational age). Two-sample hypothesis tests applied for comparisons of having or not having the corresponding genotype. Results presented as mean ± standard deviation.

	αα/αα		αα/−α3.7		−α3.7/−α3.7	
	Mean ± SD	p-Value (αα/αα vs other genotypes)	Mean ± SD	p-Value (αα/−α3.7 vs other genotypes)	Mean ± SD	p-Value (−α3.7/−α3.7 vs other genotypes)
RBC (10^{12}/L)	2.45 ± 0.64	**0.017**	2.53 ± 0.49	0.612	3.06 ± 0.44	**<0.001**
HGB (g/dL)	7.07 ± 1.15	0.215	7.21 ± 1.00	0.938	7.66 ± 0.99	0.076
HCT (%)	20.42 ± 3.52	**0.049**	21.06 ± 3.15	0.993	23.56 ± 3.10	**0.002**
MCV (fL)	86.37 ± 16.23	0.163	84.55 ± 9.62	0.999	77.51 ± 9.28	**0.029**
MCH (pg)	29.80 ± 4.88	**0.006**	28.76 ± 3.66	0.929	25.09 ± 1.77	**<0.001**
MCHC (g/dL)	34.73 ± 2.16	0.132	34.31 ± 1.79	0.417	32.56 ± 2.06	**<0.001**
WBC (10^9/L)	12.09 ± 8.57	0.263	12.30 ± 8.77	0.491	7.52 ± 4.59	**0.005**
PLT (10^9/L)	294.49 ± 151.38	0.453	323.03 ± 160.65	0.120	245.73 ± 91.93	0.240
GLU (mg/dL)	54.76 ± 20.51	0.746	55.88 ± 26.44	0.936	51.78 ± 25.85	0.717
TBIL (mg/dL)	1.64 ± 1.16	0.062	1.47 ± 1.27	0.850	0.74 ± 0.41	**0.007**
DBIL (mg/dL)	0.62 ± 0.50	0.054	0.48 ± 0.38	0.564	0.29 ± 0.23	**0.034**
ALT (U/L)	17.33 ± 16.38	0.481	22.21 ± 38.46	0.683	10.81 ± 7.55	0.098
AST (U/L)	46.34 ± 37.24	0.208	52.10 ± 98.11	0.347	40.21 ± 25.79	0.619
CREAT (mg/dL)	0.44 ± 0.15	0.750	0.45 ± 0.20	0.744	0.42 ± 0.19	1
UREA (mg/dL)	12.48 ± 7.07	0.368	11.15 ± 4.52	0.926	9.44 ± 5.53	0.145
LDH (U/L)	687.82 ± 443.02	0.749	759.30 ± 569.54	0.759	600.05 ± 234.69	0.978

αα/αα – homozygous with no −3.7 kb α-thalassemia deletion, αα/−α3.7 – heterozygous for 3.7 kb α-thalassemia deletion, −α3.7/−α3.7 – homozygous for −3.7 kb α-thalassemia deletion, RBC – erythrocytes, HGB – total hemoglobin, HCT – hematocrit, MCV – Mean corpuscular volume, MCH – mean corpuscular hemoglobin, MCHC – mean corpuscular hemoglobin concentration, WBC – white blood cell count, PLT – platelets, GLU – glucose, TBIL – total bilirubin, DBIL – direct bilirubin, ALT - Alanine Aminotransferase, AST – aspartate aminotransferase, CREAT – creatinine, LDH - Lactate Dehydrogenase.
Bold values indicate statistical significance ($p < 0.05$).

Table 3
HBB haplotype distribution.

HBB haplotype	N	%
CAR/CAR	141	87.0%
CAR/BEN	11	6.8%
CAR/SEN	4	2.5%
CAR/UNK	4	2.5%
BEN/BEN	1	0.6%
BEN/UNK	1	0.6%

SEN - Senegal, BEN – Benin, CAR- Central African Republic or Bantu, UNK - unknown.

Table 4
Hematological and Biochemical parameters of the SCD pregnant women, grouped by HBB haplotype (20th to 28th week gestational age). Values presented as mean ± standard deviation. P-values correspond to the two-sample hypothesis tests.

	CAR/CAR	Other haplotypes	p-Value
RBC (10^{12}/L)	2.52 ± 0.58	2.86 ± 0.59	**0.023**
HGB (g/dL)	7.09 ± 1.05	7.94 ± 1.03	**0.002**
HCT (%)	20.80 ± 3.39	22.97 ± 3.29	**0.014**
MCV (fL)	84.90 ± 13.61	82.10 ± 11.57	0.450
MCH (pg)	28.86 ± 4.43	28.43 ± 4.01	0.588
MCHC (g/dL)	34.24 ± 2.10	34.70 ± 2.15	0.674
WBC (10^9/L)	11.66 ± 8.85	11.53 ± 3.88	0.554
PLT (10^9/L)	299.97 ± 151.79	300.26 ± 144.71	0.912
GLU (mg/dL)	54.46 ± 24.40	56.99 ± 17.84	0.513
TBIL (mg/dL)	1.51 ± 1.22	1.22 ± 0.82	0.477
DBIL (mg/dL)	0.52 ± 0.44	0.52 ± 0.40	0.783
ALT (U/L)	19.26 ± 28.76	12.95 ± 7.93	0.642
AST (U/L)	49.36 ± 71.83	37.71 ± 20.58	0.533
CREAT (mg/dL)	0.45 ± 0.18	0.40 ± 0.13	0.587
UREA (mg/dL)	11.62 ± 6.25	11.12 ± 4.43	0.959
LDH (U/L)	739.45 ± 488.50	472.35 ± 285.61	**0.027**

(RBC – erythrocytes, HGB – total hemoglobin, HCT – hematocrit, MCV – Mean corpuscular volume, MCH – mean corpuscular hemoglobin, MCHC – mean corpuscular hemoglobin concentration, WBC – white blood cell count, PLT – platelets, GLU – glucose, TBIL – total bilirubin, DBIL – direct bilirubin, ALT - Alanine Aminotransferase, AST – aspartate aminotransferase, CREAT – creatinine, LDH - Lactate Dehydrogenase)
Bold values indicate statistical significance ($p < 0.05$).

The lower ratio of prostacyclin-thromboxane in SCD pregnant women, and its association with increased vasoconstriction, could be an explanation for this high rate [27,28]. Although the loss to follow-up undermines the possibility of calculating a true pre-eclampsia rate, the values registered in this cohort are worrying, being more than twice the European values.

Regarding maternal mortality, estimates point to a maternal mortality ratio (MMR) in SSA in 2023 of 447 deaths per 100.000 livebirths [29], which reflects 1 death per 223.7 livebirths. In this cohort, 1 maternal death was registered at the time of delivery, in only 50 deliveries that were registered at MLP. Evidently, it is impossible to compare these results with the estimates due to the high loss to follow up. Nevertheless previous studies already showed a significantly higher risk of maternal death in SCD patients compared to non SCD patients, particularly relevant in LMIC [14].

In total severe maternal complications were registered in 68% of deliveries (34 in 50). These numbers highlight the urgent need to give these women close and individualized care during pregnancy.

6. Fetal outcomes

Premature birth is a concern in SCD pregnancy. In the present study, 65.5% of births happened before 37 weeks of gestation. Preterm birth estimates from 2020 for SSA point to a 10.1% [8.5–12.7%] rate. [30] These values may be inaccurate as the systematic and methodical collection and management of medical data remains, although improving in recent years, largely unimplemented in LMIC. The substantially higher value in this cohort is likely influenced by the high loss to follow-up; still, it underscores the huge impact of SCD on premature births, as already been shown in previous studies, with a proportion of prematurity that can be five times higher in SCD patients compared to non-SCD patients [26] Prematurity is a risk factor for under-five mortality, which is especially high in Angola and SSA (64 per 1000 live births and 68 per 1000 live births, respectively) [31], as it correlates

with development and intellectual disabilities, as well as other complications [30].

In parallel to prematurity, low birth weight (LBW) is also a severe outcome in pregnancy in SCD. WHO defines LBW as under 2.5Kg [24], and estimates indicate a mean frequency of LBW of 13.9 (12.5–15.6) in SSA in 2020 [32]. In the present study, the mean birthweight was 2.49 ± 0.46, which indicates that more than 50% of babies were born with LBW. If we consider only the full-term babies, the mean increases to 2.63 ± 0.36, corresponding to 33% of babies born with LBW. Former studies had already demonstrated that SCD women had twice the risk of having a LBW baby [14], nevertheless, the rate of LBW in this cohort is substantially higher than reported values in European countries [26,33].

These exceptionally high values of prematurity and LBW highlight the urgent need to implement postnatal follow-up consultations to monitor the development and thriving of these babies.

7. The influence of genetic variability

In the present study HBB haplotypes and the presence of −3.7 kb α-thalassemia deletion was determined.

Women with the CAR/CAR haplotype presented significantly lower hemoglobin, RBC, and HCT (Table 4). Also, more cases of moderate to severe jaundice were registered, and LDH values were higher, which is suggestive of greater hemolysis. These results align with previous studies that indicate that CAR is the most severe phenotype [8,34].

Conversely, the coinherence of −3.7 kb α-thalassemia deletion showed, as expected, to be an advantage in SCD, regarding hematological and biochemical indices (Table 2). Homozygous for the deletion presented significantly higher values of RBC and HCT. The lower levels of MCV, MCH, and MCHC indicate smaller erythrocytes, with a lower hemoglobin content, which reduces hemoglobin polymerization [35]. Markers of hemolysis also improved in the presence of the deletion. LDH values were lower, although not statistically significant, and in terms of jaundice, more moderate to severe cases were identified in the homozygous with no deletion (p-value = 0.007). In fact, several authors have already mentioned that α-thalassemia increases erythrocyte lifespan and decreases hemolysis, being associated with fewer common hemolytic complications of SCD [11,36].

Although these clinical and analytical differences between HBB haplotypes and − 3.7 kb α-thalassemia deletion genotypes, no statistically significant differences were found for pre-eclampsia. The single recorded maternal death involved a woman with the CAR/CAR genotype who did not carry the −3.7 kb α-thalassemia deletion.

Concerning fetal outcomes, homozygous women for the −3.7 kb α-thalassemia deletion presented a higher rate of livebirths than other genotypes, and CAR/CAR women had a 9.5 times higher odds of having a premature birth. These results align with the phenotypical heterogeneity and tendency for severity already shown in the clinical and analytical indices.

7.1. Strengths and limitations

The present study was conducted at one of the biggest maternity hospitals in Luanda, Angola. To the best of our knowledge, this was the first study performed with pregnant women with SCD in this region, where the estimated prevalence of this disease is extremely high. Also, although some scientific literature available addresses the role of SCD in pregnancy, most of the studies were conducted in high-income countries, where healthcare systems provide closer and continued care to patients.

The main limitations of this study were the marked loss to follow up and unavailability of complete records. In Angola, as in many LMIC, regular medical follow-up during pregnancy is not routinely available. This issue is not merely economic, but equally cultural. Women only seek medical support after a complication or at an advanced stage of pregnancy, as evidenced by the small number of recruited pregnant women in the first trimester (Fig. 1), and some still deliver their babies at home. Possibly, some of these women sought medical care in other facilities. Also, systematic methods for gathering and managing medical data are lacking. Together, these factors led to a notable decrease in follow-up rates and data incompleteness in our study, which hindered the possibility of accurately calculating key rates, such as miscarriages in recent pregnancies or even maternal death, and comparing rates with those reported in other populations. Nevertheless, the results presented here are alarming.

Several guidelines have been published regarding SCD and other hemoglobinopathies management, with recommendations to be applied to pregnant women [37–39]. However, the limited resources to implement them remain a major concern for LMIC. There is an urgent need for health system strengthening and investment in patient care, health workers' training, and research, as the healthcare disparities between high-income and LMIC certainly influence the rate of outcomes in SCD pregnancy.

Health literacy should also be considered a priority to create awareness about the disease, to reduce the stigma patients face, and to increase adherence to treatments and care. In terms of pregnancy, pre-counseling consultations and baseline assessments should be promoted. Regular medical appointments should be encouraged so that complications in pregnancy can be prevented or managed early, and women must be informed about the complications and outcomes of pregnancy with SCD. Also, early identification of the more severe phenotypes is essential. Medical teams should be multidisciplinary and not just limited to gynecologists/obstetricians. Close and early individualized care increases the chances of successful pregnancies. In fact, a prospective control study in Nigeria compared outcomes from SS women and AA women, and although SS women presented a higher complication rate, they stated that, if close and early individualized care is provided to SS women, pregnancy outcomes might be comparable [28].

8. Conclusions

Pregnancy in SCD is associated with an increase in severe outcomes for both mother and baby. Previous studies have shown a higher incidence of eclampsia/pre-eclampsia, preterm birth, LBW, and maternal/fetal death. In Angola, systematic approaches for the collection and management of medical data are still lacking, which makes it challenging to infer rates of these outcomes in SCD. In this study, we intended to identify severe outcomes and complications in a cohort of SCD Angolan pregnant patients and evaluate the influence of the HBB haplotypes and co-inheritance of α-thalassemia. Despite the limitations, our results corroborate previous studies pointing to high rates of severe complications during pregnancy in SCD. Also, we showed that co-inheritance of −3.7 kb α-thalassemia not only improves hematological indices, as already demonstrated in previous studies, but also that homozygous women had over four times higher odds of having a livebirth than the other genotypes. In what concerns HBB haplotypes, CAR/CAR women had above 9 times higher odds of having a premature birth. More studies are required, with closer and effective follow-up, to evaluate the real incidence rates of pregnancy complications in SCD, to help identify the most severe phenotypes, and to demonstrate the effectiveness of individualized and close care. Also, these studies should include postnatal follow-up consultations, as several complications may occur postpartum [40] and the newborn's development and thriving should be monitored.

Further research is needed to evaluate the impact of SCD during pregnancy, especially in LMIC, to investigate preventive and affordable strategies for early complications, enable early identification of the more severe phenotypes, and provide individualized treatment, to ultimately reduce maternal and fetal mortality.

CRediT authorship contribution statement

Catarina Ginete: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Carolina Cruz:** Writing – review & editing, Methodology, Investigation. **Mariana Delgadinho:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Manuela Mendes:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Fernanda Simão:** Writing – review & editing, Methodology, Investigation. **Lígia Alves:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Jocelyne Vasconcelos:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Paula Borralho:** Writing – review & editing, Supervision, Methodology. **Miguel Brito:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Ethical approval

This study was conducted according to the guidelines of the Declaration of Helsinki. It was approved by the Ethical Committee of the Ministry of Health of Angola (CE_ N°09/2021) and the Ethical Committee of Escola Superior de Saúde de Lisboa (CE-ESTeSL_N°. 23-2021). Informed consent was obtained and signed by all patients.

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Declaration of competing interest

The authors declare that they have no competing interests. The funders had no role in the study's design; collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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Data availability

The data supporting this study's findings are available from the corresponding author (M.B.) upon reasonable request.

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