



**Original Article**

**Homozygous Deletion Alpha-Thalassemia and Hereditary Persistence of Fetal Hemoglobin, Two Genetic Factors Predictive the Reduction of Morbidity and Mortality During Pregnancy in Sickle Cell Patients. A Report from the Democratic Republic of Congo**

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**Competing interests:** The authors have declared that no competing interests exist.

**Abstract. Objective:** to determine the beneficial role of Fetal Hemoglobin (FHb) and alpha-thal on fetal and maternal morbidity during pregnancy in sickle cell patients.

**Study site:** the study was conducted at the sickle cell center of Kinshasa between 2008 and 2018

**Setting and study population:** this is a documentary and analytical study that included 980 deliveries of homozygous sickle cell patients.

**Methods:** the diagnosis of SCD and the quantification of FHb were performed with the capillary electrophoresis technique. The molecular test confirmed the diagnosis of SCD. The diagnosis of alpha-thal was made with the multiplex ligation-dependent probe amplification (MLPA) technique. Sickle cell pregnancies were followed according to the protocol of care in force in the University of Kinshasa Hospital service. The variables of interest were: hematological variables, sickle cell crises during pregnancy, maternal and fetal complications.

**Statistics:** statistical analyses were performed with SPSS 20.0 software. Means and standard deviations were compared with the Student's t and ANOVA tests. The value of  $p < 0.05$  was considered the significance level.

**Results:** the Hb-SS / alpha-thal and HbSS / HPFH genotypes were observed in 101 and 121 women, respectively. Otherwise, 758 women had HbSS genotype. The morbidity related to sickle cell complications in the mother and fetus were less frequent in the Hb-SS / alpha-thal and HbSS / HPFH groups than in HB-SS group. The differences were statistically significant.

**Conclusion:** this study showed a significant protective effect of alpha-thal and HPFH during pregnancy in sickle-cell pregnant women.

**Keywords:** Alpha-thal, HPFH, Morbidity, Pregnancy, Sickle cell disease.

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**Introduction.** Sickle cell disease (SCD) is a constitutional hemoglobinopathy with autosomal recessive inheritance. The characteristic of this mutation is a transversion of a purine base [A] by a pyrimidine base in the beta-globin gene. The consequence of this mutation is the substitution of glutamic acid by valine at position 6 in the beta globin chain.<sup>1,2</sup> The substitution of a hydrophilic amino acid (glutamic acid) by a hydrophobic amino acid (valine) results in the production of abnormal hemoglobin called HbS. Indeed, in concentrated solution and under the influence of a decrease in oxygen partial pressure, HbS undergoes a supramolecular polymerization process.<sup>3</sup> Hemoglobin S is today the most widespread structural abnormality of hemoglobins in the world.<sup>4,5</sup> Equatorial Africa is the area of maximum incidence. Clinically SCD is characterized by recurrent vaso-occlusive ischemic events, chronic hemolysis, and high susceptibility to infections. The best management begins with early detection, preventive care against encapsulated bacterial infections and especially the administration of hydroxyurea. The association of SCD and pregnancy is characterized by high maternal and fetal morbidity.<sup>6,7</sup> Indeed, it is well established that there is a reciprocal influence between pregnancy and SCD. During pregnancy, there is a worsening of maternal anemia, an increase in the frequency of VOC, and a high risk of infection.<sup>8</sup> The fetus is at high risk of spontaneous abortions, prematurity, intrauterine growth retardation, hypotrophy, and in utero death.<sup>9-11</sup> Genetically, two factors showed their modulatory effect on the sickle cell phenotype. These are fetal hemoglobin (FHb:  $\alpha_2\gamma_2$ ) and alpha-thalassemia. A high level of FHb slows down the polymerization, which results in a reduction of the number of VOC and hemolysis. The mechanism of this protection is explained by the formation of hybrid polymers ( $\alpha_2\beta^S\gamma$ ) that stop the growth of the phenomenon of polymerization. This property has since been used in the treatment of SCD following empirical evidence that hydroxyurea stimulated the production of FHb.<sup>12,13</sup> The protective effect of alpha-thalassemia is related to the reduction of Hb concentration in the erythrocytes, which results in the microcytic anemia.<sup>14</sup> Indeed, Mikobi et al. showed that homozygous alpha-thalassemia and an FHb level > 15% had a protective effect on SCD in Congolese patients.<sup>15</sup> The objective of the present study was to determine the beneficial role of genetic modulating factors of sickle cell disease in fetal and maternal morbidity and mortality during pregnancy in sickle cell patients.

### **Patients and Methods.**

**Subjects.** In this is a transversal study, 980 records of SCD pregnant women, who gave birth between 2008 and 2018, were analyzed. The review was conducted at the Sickle Cell Center in Kinshasa, Democratic

Republic of Congo (DRC). The patients were divided into three genotypic subgroups. The first subgroup consisted of SCD pregnant with associated homozygous alpha-thalassemia (Hb-SS/alpha-thal), the second group consisted of SCD with hereditary persistence of fetal hemoglobin (HbSS / HPFH), and the third group consisted of gestants without association with one of the two pathologies mentioned above (HbSS).

**Operational definitions.** In this study, the group of gestational Hb-SS /alpha-thal included only patients who had the deletion alpha-thalassemia homozygous ( $-\alpha$ ,  $-\alpha$  or  $--$ ,  $\alpha\alpha$ ) and the group HbSS / HPFH the patients with an FHb level > 15%. However, all sickle cell patients with heterozygous alpha-thalassemia ( $-\alpha$ ,  $\alpha\alpha$  or  $\alpha\alpha$ ,  $-\alpha$ ) or with FHb < 15% were excluded from this study.

**Laboratory tests.** The diagnosis of SCD was made by the technique of capillary electrophoresis; the device used was the Mini cap flex piercing (Sebia, France). This technique also made it possible to quantify the fraction of FHb and to make the diagnosis of HPFH. The diagnosis of HPFH was retained for an FHb > 15% after three dosages within three months. The diagnosis of SCD was confirmed by a molecular test based on the restriction fragment-length polymerization technique (RFLP). The diagnosis of alpha-thalassemia has been made by the Multiplex Ligation-dependent Probe Amplification (MLPA) technique. The procedures, as well as the reagents used for both techniques (RFLP and MLPA), have been carefully described by Mikobi et al..<sup>15,16</sup>

### **Protocol for the management of sickle cell disease.**

**Transfusion and pain management.** Our protocol advocates only therapeutic transfusions during pregnancy. Prophylactic transfusions which systematically transfuse sickle cell disease from the 24th weeks of pregnancy are not practiced in our department for two main reasons: economic and lack of consensus in the real benefit of systemic prophylactic transfusion. However, we will resort to occasional transfusion exchanges during the pregnancy when there is an indication. Vaso-occlusive pain at levels 1 and 2 was managed with analgesics according to the recommendations of the WHO. Complicated VOC with Stage 3 pain was managed with a multidisciplinary team consisting of anesthesia intensive care and hematologist.

### ***Maternal pregnancy supplements and fetal monitoring.***

All pregnant women were given a systematic supplementation of iron and folic acid, and antioxidants (omega 3 fatty acids and magnesium pidolate) from the 12th week of amenorrhea. Prophylactic anti-

malarial treatment was given between the 24th and 32nd weeks, and anti-helminthic deworming was given between 28 and 32 weeks. No patients received hydroxyurea during pregnancy. Fetal surveillance was primarily based on ultrasound scans.

**Childbirth.** Delivery was systematically scheduled for the 37th week of amenorrhea after the completion of the biophysical manning score.

**Variables of interest for the study.** In this study, the following general maternal variables were assessed: gestational age, menarche age, parity, weight gain. The pregnancy weight gain ( $\Delta P$ ) was calculated from the following formula:  $\Delta P = Pf - Pi$  ( $Pf$  weight of the pregnant woman at the time of delivery,  $Pi$  weight before pregnancy). The evolution of the Hb rate allowed to appreciate the validity of a punctual transfusion. Maternal morbidity was assessed by the analysis of sickle cell complications: VOC and hemolysis as a function of gestational age, including pregnancy complications: preeclampsia, acute chest syndrome (ACS), parasitic infections (malaria), bacterial infections (urinary tract infections, pneumonia, sepsis) and postpartum, endometritis. Fetal morbidity was assessed by analysis of abortion rates, prematurity, low birth weight, and in utero death.

**Statistical analyses.** Statistical analyses were performed using SPSS version 20.0.T. (2016). We had

determined the distribution of the study population, which was normal. We have determined also means and standard deviations. Mean of two groups were compared by the Student's t-test and those of three groups by the ANOVA test. The value of  $p < 0.05$  was considered the only one of significance.

**Results.** Our study showed that 101 (10.30%) of our sickle cell deliveries had a homozygous alpha-thal deletion, while 121 (12.34%) of the women had an HPFH. Besides, 758 or 77.34% of the deliveries had none of the two associated genetic factors.

**Table 1** gives the general characteristics of sickle-cell pregnancies according to their genotype. The analysis in the table shows that the Hb-SS / alpha-thal and HbSS / HPFH women had their menarche before those of the HbSS genotype. In addition, these gestants (HbSS/alpha-thal and HbSS/HPFH) had a better weight gain. Statistical differences between the first two groups and the third group were highly significant ( $p < 0.001$ ).

**Table 2** shows the biological variables during pregnancy. From the analysis in this table, the gestants of the HbSS genotype had higher levels of WBC, platelets, and reticulocytes than those with an alpha-thal or HPFH combination. The differences were highly significant ( $p < 0.001$ ). In contrast, serum iron and Hb were similar in all three groups.

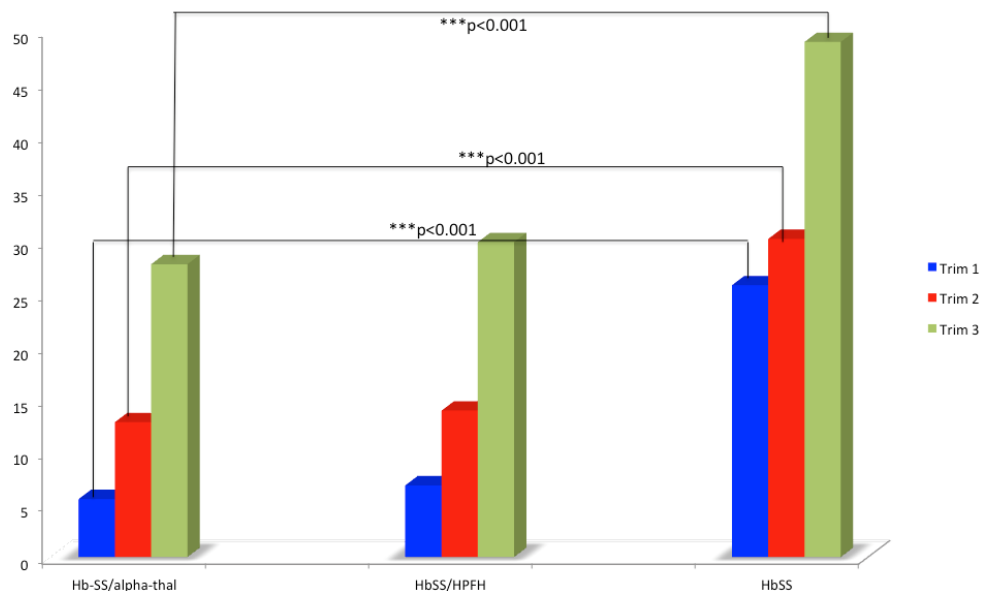
**Figure 1** shows the distribution of sickle cell crises during pregnancy. The chart analysis shows that VOC

**Table 1.** General Characteristics of Sickle Cell Pregnancy by Genotype.

Variables	HbSS/alpha-thal (n = 101)		HbSS/HPFH (n = 121)		HbSS (n = 758)		P (anova)
	Mean	SD	Mean	SD	Mean	SD	
Maternal age (year)	23.2	3.4	24.6	2.5	20.9	1.2	0.06
Menarche age (year)	12	1.2	13	1.4	16	1.9	<0.001
Parity (n)	2	1.5	3	1.5	2	1.5	0.09
Gestational age (weeks)	37	1.9	36	1.5	35	2.2	0.06
Gravitational weight gain (Kg)	6.2	1.1	5.4	1.9	3.1	1.4	<0.001

**Table 2.** The biological variables of the pregnant.

Variables	HbSS/alpha-thal (n = 101)		HbSS/HPFH (n = 121)		HbSS (n = 758)		P (anova)
	Mean	SD	Mean	SD	Mean	SD	
Hemoglobin (g/dl)	6.5	1.1	9.5	1.9	7.1	2.2	0.05
WBCs ( $\times 10^3/\mu\text{l}$ )	8.1	0.2	6.5	0.9	15.7	1.3	<0.001
Platelets ( $\times 10^3/\mu\text{l}$ )	250.35	111.1	272.44	102.4	360.41	134.6	<0.001
Reticulocytes (%)	7.56	2.34	9.74	4.11	15.47	7.27	<0.001
Serum iron ( $\mu\text{mol/l}$ )	15.75	2.65	18.5	4.2	17.7	3.4	0.08



**Figure 1.** Evolution of VOC and worsening of anemia during pregnancy.

**Table 3.** Frequencies of maternal and fetal complications.

Complications	HbSS/alpha-thal (n = 101)		HbSS/HPFH (n = 121)		HbSS (n = 758)		P (anova)
	Mean	SD	Mean	SD	Mean	SD	
<b>Pulmonary complication ACS (%)</b>	8.4	1.2	9.2	1.4	12.1	1.2	0.12
<b>Preeclampsia (%)</b>	9.2	0.9	4.2	1.5	10.5	3.6	<0.001
<b>Abortion (%)</b>	5.2	0.9	4.2	1.5	10.5	3.6	<0.001
<b>Prematurity (%)</b>	12.7	2.1	14.1	1.9	22.2	2.9	<0.001
<b>Fetal weight (g)</b>	2850.9	250.2	2950.5	655.2	2350.8	222.4	<0.001
<b>Death in utero (n)</b>	2	0.2	4	0.4	25	1.2	<0.001
<b>Maternal Death (n)</b>	1	0.2	1	0.1	15	0.5	<0.001

and hemolysis increase steadily with gestational age. They reach their maximum in the third trimester. However, the HbSS genotype is more affected than the other two groups. Statistical differences with the HbSS/alpha-thal group are highly significant ( $p < 0.001$ ).

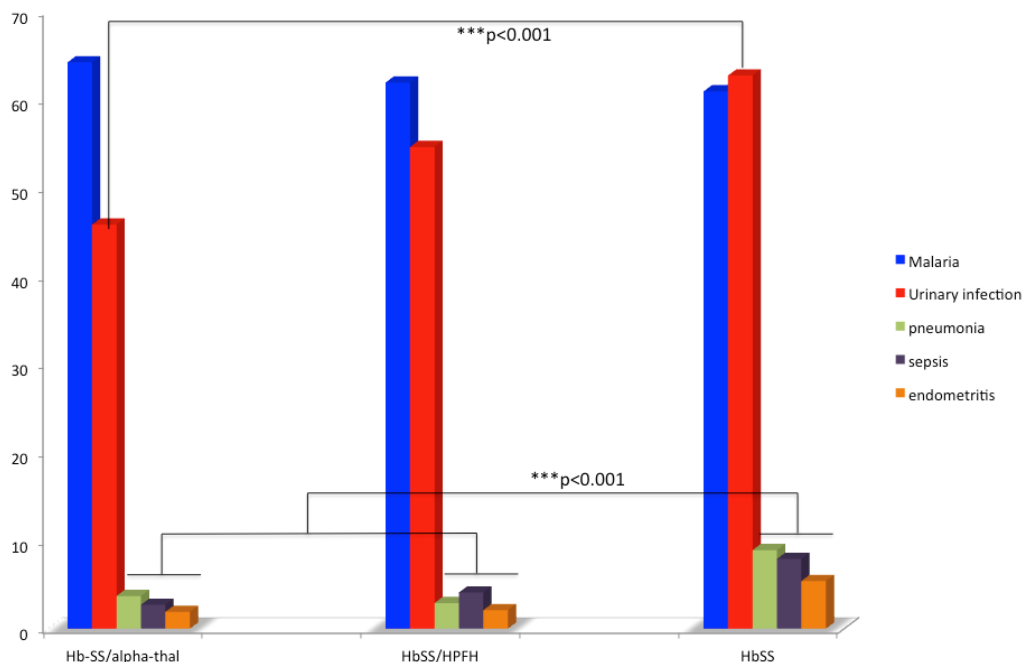
**Table 3** presents the frequencies of maternal and fetal complications. The analysis in this table shows that the frequencies of ACS and pre-eclampsia were similar in all three groups. In contrast, spontaneous abortions, prematurity, low birth weight, in utero death and maternal death have been more observed in the HbSS genotype. Statistical differences with the other two genotypes were highly significant ( $p < 0.001$ ).

**Figure 2** shows the distribution of parasitic and bacterial infections during pregnancy. It appears that the frequencies of malaria were similar in the three groups. In contrast, bacterial infections (urinary tract infections, pneumonia, sepsis, and endometritis) were more common in the HbSS genotype. The statistical differences were highly significant ( $p < 0.001$ ).

**Delivery route.** In our series, 49% of Caesarean sections were performed in patients with the HbSS genotype. Whereas the rates of the cesarean section of pregnant women with the HbSS / alpha and HbSS / HbF genotypes were 24% and 27% respectively.

**Discussion.** Fhb and alpha-thal are recognized as modulatory factors for the clinical expression of SCD.<sup>17</sup> However, their beneficial effect during pregnancy is not well known in subtropical Africa.

In this study, sickle cell patients with HbSS genotypes had their menarche late at 16 years of age. Puberty delay is usually observed in SCD and is proportional to the severity of the disease.<sup>18</sup> The delivery was programmed at the 37th week; this attitude is the one reported by many authors.<sup>19,20</sup> Our study showed a significant difference in weight gain in favor of the HbSS / PHFH and HbSS / alpha-thal genotypes. The observed difference could be associated



**Figure 2.** Distribution of parasitic and bacterial infections during pregnancy.

with the protective effects of HbF<sup>21</sup> and alpha-thal.<sup>22</sup> From the hematological variables, the HbSS genotype has a high number of WBCs, reticulocytes, and platelets. These high biological variables can explain the high morbidity of these patients during pregnancy.

VOC episodes were the leading cause of morbidity during pregnancy in SCD, as also reported by other authors.<sup>23</sup> These VOC increase with gestational age and are more frequent and severe in the perinatal period. In our series, VOC seizures were more common in the HbSS group. During pregnancy, several authors report a high frequency of complications such as acute thoracic syndrome and pre-eclampsia.<sup>23,24</sup> Their frequencies (9 to 16%) vary from one series to another.<sup>20,23,24</sup> In our series, the frequencies of these two complications are similar to those reported by other authors on the one hand and similar between the three genotypes on the other hand. During pregnancy, spontaneous abortions, prematurity, hypotrophy, and in utero fetal death are the main complications found in SCD.<sup>20,25</sup> The frequencies are different from one series to another; they are also proportional to the severity of the disease during pregnancy. In our series, these complications are more common in the HbSS group.

Infection is ranked as the second leading cause of morbidity during pregnancy in SCD. In our series, malaria was the first parasitic infection encountered because of the geographical situation of DRC. Indeed, DRC is located in the area with the highest prevalence

of malaria. This infection alone constitutes the first cause of maternal and fetal morbidity.<sup>26</sup> In tropical Africa, malaria is ranked as the leading cause of fetal hypotrophy. The high morbidity of malaria during pregnancy is associated with maternal anemia that *Plasmodium falciparum* can cause.<sup>27</sup> In our series, the frequency of malaria was similar in all three genotypes. Maternal morbidity has also been influenced by bacterial infections such as urinary tract infection, pneumonia, sepsis, and endometritis. Their frequencies are similar to those reported by other authors.<sup>20</sup> However, in our series, these infections were more common in the HbSS group. The high frequency of cesarean section in SCD is related to peripartum complications. In our series, 49% of pregnant women had delivered by cesarean section. This frequency is similar to those reported by other authors.<sup>20</sup> However, the group with the HbSS genotype was more exposed to cesarean section than the other two. The protective effect of HbF and alpha-thal observed in our series, is similar to that reported by other authors in the associations S/β(0) thalassemia, S/β(+) thalassemia,<sup>21</sup> or other major sickle cell syndromes like SC, SD.

**Conclusions.** Homozygous alpha-thal and PHFH have shown their protective effect on sickle cell disease in general. This study shows that these genetic factors modulating sickle cell phenotype can significantly reduce maternal and fetal morbidity during pregnancy.

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