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Early Morbidity and Mortality in Neonates of Mothers with Sickle Cell Disease at the Borgou/Alibori Center Departmental Teaching Hospital in Benin

Alphonse Noudamadjo[1], Falilatou Agbeille Mohamed[1], Médétinmè Kpanidja Gérard[1], Mahublo Voduhe[1], Justin Chogou[1], Guedenon Romulus[2], Julien Didier Adedemy[1], Joseph Agossou[1]

[1]Faculty of Medicine, Mother and Child Department, University of Parakou, Parakou, Benin
[2]National Training School for Senior Technicians in Public Health and Surveillance, University of Parakou, Parakou, Benin
Email: fmagbeille@yahoo.fr

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Abstract

Introduction: Association of sickle cell disease and pregnancy is a risky situation for both the mother and neonate. **Objective**: To determine the early morbidity and mortality among neonates of mothers with sickle cell disease at Borgou/Alibori Center Departmental Teaching Hospital (CHUD B/A) in Benin. **Patients and Methods**: This was a descriptive and analytical observational study conducted at CHUD-B/A from January 1, 2015, to August 31, 2019. It included pregnant women with sickle cell disease who gave birth to a liveborn neonate at the term of at least 28 weeks of amenorrhea. Variables studied were sociodemographic, clinical, and evolutionary. Analysis of the factors associated with early death was also carried out with a significance threshold set at $p < 0.05$. **Results**: Out of a total of 119 pregnant women, 95 neonates were recorded. Main morbidities were: prematurity and intrauterine growth restriction (49.5%); respiratory distress (40%), bacterial infection (30.5%), and perinatal asphyxia (21.1%). Early mortality rate was 8.4%. In bivariate analysis, the factors associated with early death were: parity ($p < 0.001$), the severity of maternal anemia ($p < 0.008$), birth weight under 1500 g ($p < 0.002$), the birth term under 32 weeks of amenorrhea ($p < 0.001$), resuscitation for at least 5 minutes ($p = 0.001$). In multivariate analysis, resuscitation for at least 5 minutes ($p = 0.007$) was mainly associated with early death. **Conclusion**: One out of two neonates of mothers with sickle cell disease has a low birth weight. Early mortality is high due to perinatal asphyxia. Hence the multidisciplinary care of these mothers.

Keywords

Early, Morbidity, Mortality, Neonates, Mothers, Sickle Cell Disease, Benin

1. Introduction

Sickle cell disease is the first and most widespread genetic disease in the world. It is characterized by the presence of abnormal hemoglobin (hemoglobin S) in red blood cells causing sickling, vaso-occlusion, and chronic hemolytic anemia. Three sickle cell syndromes are classically described: homozygosity SS and composite heterozygosity SC and Sβ thalassemia [1]. It is a growing public health problem with an increased risk of morbidity and mortality. Estimates suggest that each year, about 300,000 children are born with sickle cell disease and that number could reach 400,000 by 2050 [1] [2] [3]. The majority of patients are in Sub-Saharan Africa where the disease is often fatal before the age of 5 years [4]. Due to therapeutic progress, their survival has improved, allowing more and more pregnancies in women who are affected [5]. However, the association of pregnancy and sickle cell disease is a high-risk situation for the mother as well as the fetus and the neonate [6]. Fetal complications include, among others, growth restriction (IUGR), acute fetal distress, premature delivery, and increased perinatal mortality [7] [8]. In Sub-Saharan Africa, the management of these pregnant women is a major challenge because the risk of complications is higher. The Republic of Benin, in West Africa, has a high prevalence of sickle cell disease. Although there are no precise data on the incidence of pregnancies in women with this condition, they are not by far as frequent since the prevalence of S gene carriers is around 25% [9]. A tiny number of these pregnant women have access to specialized care in the country. The Borgou/Alibori Center Departmental Teaching Hospital (CHUD B/A) is a reference hospital in northern Benin where the data about the morbidity, early mortality and factors associated to deaths in neonates of these pregnant women are not known. The objective of this study was to determine the early morbidity and mortality in neonates of mothers with sickle cell disease at Borgou/Alibori Center Departmental Teaching Hospital (CHUD B/A) at Parakou in northern Benin in order to improve their management.

2. Patients and Methods

This was a descriptive and analytical observational study conducted in maternity and neonatology departments at the Borgou/Alibori Center Departmental Teaching Hospital (CHUD B/A) from January 1, 2015, to August 31, 2019.

All pregnant women with a major sickle cell syndrome (SS, SC, and Sβthal) meeting the following criteria were included:

- Whether or not you have followed your pregnancy at the CHUD-B/A maternity ward. As far as the place of pregnancy follow-up is concerned, there is a specialized center for the management of sickle cell patients: the Center for In-

tegrated Medical Health Care of Infants and Pregnant Women with Sickle Cell Disease (CPMINFED), but pregnancies may have been also followed in other structures such as CHUD-B/A maternity or other public or private maternities in the city of Parakou and surroundings

- Having given birth at CHUD-B/A maternity ward after 28 weeks of amenorrhea (WA) and more than one live born neonate.

- Having a complete medical record means providing: general information about the pregnant woman, medical history related to sickle cell disease, gyneco-obstetrical history, information on the current pregnancy course, acute complications that occurred during pregnancy; information about the childbirth course.

- Having a complete medical record for the neonate includes information on the clinical condition of the neonate since birth, his anthropometric parameters, the morbidities presented, and his vital status before seven completed days of life.

Excluded from the study, were pregnant women with:

- Incomplete medical records and those of their neonates.

- Comorbidities: HIV infection, diabetes.

Pregnancy was considered well followed up when the pregnant woman had at least 8 quality prenatal consultations as recommended by WHO [10].

Anemia among mothers was considered severe for a hemoglobin level below 7 g/dl according WHO criteria. Early neonatal death was defined as any death of a neonate with a gestational age of 28 WA and more, alive at birth and who died between 0 and 7 completed days of life. The neonatal mortality rate was the number of early neonatal deaths per thousand live births [11].

The sampling consisted of an exhaustive census of pregnant women meeting our inclusion criteria. The dependent variables were the existence of morbidity and early neonatal death. The independent variables were sociodemographic, clinical, and evolutionary in neonates.

The early neonatal prognosis was good when the pregnancy resulted in the birth of a neonate of 28 WA and more, alive beyond seven completed days of life, and bad in the opposite case.

Data were entered and analyzed using Microsoft Excel 2013 software and Epi Info version 7.2. The significance threshold used was p (p-value) less than <0.05. For the factors associated with early neonatal deaths, a bivariate analysis was performed followed by a multivariate analysis with logistic regression. To control the confounding factors and highlight the risk factors associated with poor early neonatal prognosis, the variables whose p-value < 0.20 were included in the model. The protocol was submitted to the ethics committee of the University of Parakou and obtained its approval under the reference 0289/CLERB-UP/P/SP/R/SA.

3. Results

3.1. Frequency of Sickle Cell Disease in Pregnant Women

From January 1, 2015,to August 31, 2019, 130 pregnant women with sickle cell

disease out of a total of 10,087 pregnant women admitted at the maternity of CHUD-Borgou/Alibori were identified, *i.e.*, a frequency of 1.3%. Among them, 11 had unusable medical records. As for the remaining 119 pregnant women, 24 were excluded due to: maternal death during pregnancy (2 cases), spontaneous miscarriage (2 cases), and stillbirth (20 cases). The 95 pregnant women meeting our inclusion criteria were carriers of a single pregnancy.

Thus, among 119 pregnant women, the pregnancy resulted in 95 live births of neonates or a live birth rate of 80%.

3.2. Characteristics of Pregnant Women

The mean age of mothers was 27 ± 32 years with extremes of 16 and 41 years. Those aged between 25 and 30 years old were the most represented (43.2%). They were out of school (35.8%). Nulliparous women were the most represented with respectively 47.4% of cases. The SC-type phenotype was the most commonly encountered (75.8%) (Table 1).

Table 1. Distribution of pregnant women according to their socio-demographic characteristics, medical and obstetrical history (N = 95).

	N	%
Age range (years)		
<20	7	7.4
[20 - 25[	19	20.0
[25 - 30[	41	43.2
[30 - 35[	17	17.9
≥35	11	11.6
Level of education		
None	34	35.8
Primary	23	24.2
Secondary	28	29.5
Higher	10	10.5
Phenotype		
SS	23	24.2
SC	72	75.8
Sβthal	0	0
Parity		
Nulliparous	45	47.4
Primiparous	24	25.2
Pauciparous	24	25.2
Multiparous	2	2.2

3.3. Clinical and Evolutionary Characteristics of the Current Pregnancy

The main mode of admission to the maternity ward was a referral from a peripheral health facility for an acute complication related to sickle cell disease (52.6%). The pregnant women had carried out at least eight prenatal consultations in 15.8% of cases. Their pregnancies had been followed in private medical practice in 56.8% of cases. The main complications noted during pregnancy were: vaso-occlusive crisis (VOC) in 74% of cases, bacterial infections (40%) including mainly 92% of urinary tract infections, severe anemia (17%), gestational hypertension (11%), and eclampsia (8.4%). Intrauterine growth restriction affected 47 fetuses (49.5%) and premature rupture of membranes (PROM) was observed in 17.9% of cases. In 10.5% of cases, delivery was vaginal and by cesarean section (89.5%), of which 53.7% related to an obstetrical emergency (Table 2).

Table 2. Distribution of pregnant women according to clinical and evolutionary characteristics of the pregnancy (N = 95).

	N	%
Mode of admission		
Referral	50	52.6
Direct admission to the maternity	45	47.4
Number of prenatal consultations		
<8	15	16
≥8	80	84
Place of the pregnancy follow-up		
Maternity of CHUD-B/A	24	25.3
CPMINFED	17	17.9
Private maternity	54	56.8
Complications during pregnancy		
Vaso-occlusive crisis	70	74
Severe Anemia	16	17
Gestational Hypertension	10	11
Eclampsia	08	8.4
Severe malaria	02	2.1
Maternal bacterial infection	38	40
Acute fetal asphyxia	12	12.6
Premature rupture of membranes	17	17.9

3.4. Characteristics of Neonates

Of these neonates, 89 of 95 were admitted to neonatology (93.6%). The sex ratio was 1.02. The average birth weight was 2474.316 ± 530.15 with extremes of 1100 g and 3900 g. The average birth size was 46.07 ± 4.18 cm with extremes of 27 and 52 cm. It was a premature birth in 49.5% of cases dominated by small prematurity (31.2%). Neonates with low birth weight (<2500 g) were the most represented (54.7%) and hypotrophy affected 49.5% of them, including 97.8% with the severe form.

3.5. Neonatal Morbidities

Neonatal pathologies were dominated by prematurity and intrauterine growth restriction in equal proportions (49.5%) followed by respiratory distress (40%), bacterial infections (30.5%), jaundice (26.3%), and perinatal asphyxia (21.1%).

Regarding perinatal asphyxia, 21 neonates had been resuscitated at birth (23.1%) with an average duration of resuscitation at 5.2 ± 3.4 minutes and the extremes of 2 and 31 minutes as illustrated in Table 3.

3.6. Early Neonatal Mortality and Associated Factors

Early neonatal deaths occurred in 8 neonates (8.4%). The average age at death was 11 hours with extremes of 1 hour and 72 hours. Deaths occurred during the first two hours of life in 88% of cases (7/8). The main cause of death was perinatal asphyxia in 75% of cases (6/8). The other two deaths were related to bacterial infection and respiratory distress.

In bivariate analysis, the factors associated with death were: parity ($p < 0.001$); admission by referral to the maternity ward ($p < 0.004$), severe maternal anemia ($p < 0.008$), birth weight under 1500 g ($p < 0.002$), gestational age less than 32 weeks ($p < 0.001$), resuscitation duration greater than or equal to 5 minutes ($p = 0.001$) (Table 4). Phenotype, place of follow-up of the pregnancy and number of prenatal visits were not statistically associated with the death of neonates. No neonatal deaths were recorded among pregnant women followed at CPMINFED.

In multivariate analysis, only a duration of resuscitation greater than or equal to 5 minutes ($p = 0.007$) was associated with death (Table 5).

Table 3. Morbidities observed in neonates of mothers with sickle cell disease (N = 95).

	N	%
Prematurity	47	49.7
Hypotrophy	47	49.7
Neonatal respiratory distress	38	40%
Neonatal bacterial infection	29	30.5
Neonatal jaundice	25	26.3
Perinatal asphyxia	20	21.1
Neonatal anemia	12	12.6

Table 4. Factors associated with early neonatal mortality in bivariate analysis.

	Total	Early Neonatal Death				OR	$CI_{95\%}$	*P*
		Yes		No				
		N	%	N	%			
Phenotype								0.075
SS	23	19	82.6	4	17.4	1	-	-
SC	72	68	94.4	4	5.6	0.279	0.063 - 1.222	0.075
Parity								**0.001**
Nulliparous	45	44	97.8	1	2.2	1	-	
Primiparous	24	19	79.2	5	20.8	11.57	1.26 - 10.91	0.08
Pauciparous	24	23	95.8	1	4.2	1.913	0.11 - 32.00	0.646
Multiparous	02	1	50.0	1	50	44	1.45 - 1328.5	0.001
Mode of admission								**0.004**
Referral	50	42	84.0	8	16.0	1	-	-
Direct to CHUD B/A maternity	45	45	100.0	0	0.0	0.000	-	0.037
Severe maternal anemia								
Yes	16	12	75	4	25	1		**0.008**
No	75	75	94.9	4	5.06	0.160	0.035 - 0.727	
Gestational Age								**<0.001**
<32 WA	3	2	66.7	1	33.3	28.6	2.262 - 363.178	
≥32 WA	92	6	6.5	86	93.5	1	-	-
Birth weight								**0.002**
<1500 g	4	2	50	2	50	14.1	1.687 - 118.93	
≥1500 g	91	6	6.6	89	93.4	1	-	
Duration of resuscitation (minutes)								**0.001**
<5	14	2	14.3	12	85.7	1	-	
≥5	7	6	86.7	1	14.3	0.027	0.002 - 0.0371	

Table 5. Factors associated with early neonatal mortality in multivariate analysis.

	OR	***CI 95%***	***P***
Parity	0.717	0.402 - 1.280	0.262
Severe maternal anemia	0.326	0.669 - 1.590	0.166
Gestational Age	0.042	0.000 - 5.077	0.195
Birth weight	3.863	0.099 - 150.264	0.469
Resuscitation ≥ 5 minutes	74.435	3.22 - 1717.85	**0.007**

4. Discussion

Our study aimed to determine the early morbidity and mortality in neonates of mothers with sickle cell disease. We also identified some factors associated with

early death. This work has some biases in the sense that, for a better evaluation of the associated factors, a comparative study with unaffected pregnant women would have been more relevant for a better assessment of the factors. However, our results remain valid.

In this study, the frequency of sickle cell disease in pregnant women was 1.3%. This frequency corroborates data in the literature with an average of 0.6% to 1.4% of pregnant women with sickle cell disease [12] [13]. It is relatively low and could be explained by the poor survival of patients, especially in Sub-Saharan Africa where access to specialized care is limited with high mortality before the age of five [4].

SC phenotype was predominant in our study (75.8%), similar to the results of Rahimy *et al.* in Cotonou (Benin) [9]. Indeed, heterozygotes SC have better survival than homozygotes SS because they have a less severe phenotype and a lower frequency of acute complications, especially during the first years of life. As a result, they reach childbearing age more easily. However, they also run a real risk during pregnancy [14] [15].

Neonatal morbidities were dominated in the present work by prematurity, intrauterine growth restriction in equal proportions, respiratory distress, neonatal bacterial infection, and perinatal asphyxia.

Indeed, 49.7% of prematurity was found in our study, similar to the results of Ugboma *et al.* in Nigeria and Costa *et al.* in Brazil [16] [17]. On the other hand, Faye *et al.* in Senegal and Igala *et al.* in Gabon [18] [19] had lower frequencies with respectively 11.8% and 21.6%. d'Almeida *et al.* in 2013 [20] at the same hospital as ours, observed 20.59% of prematurity in a study on perinatal morbidity and mortality in the general population. Our results are more than double those reported by this author in the general population. The incidence of prematurity is high in pregnant women affected by sickle cell disease with varying proportions depending on the studies between 11.8% and 75.4% in Sub-Saharan Africa [18] [21]. Boafar *et al.* in a meta-analysis noted that the risk of prematurity in these neonates was twice as high as in those of mothers without sickle cell disease [7]. The exact mechanism of this phenomenon is not yet clear, but increased production of prostaglandin has been implicated [8]. Other reasons are anemia, urinary tract infections, placenta previa, and pregnancy toxemia, which are more frequently reported in these pregnant women. In this work, bacterial infections were observed in 40% of pregnant women with 92% of urinary tract infections, as well as gestational hypertension and its complications (19.4%) and severe maternal anemia (17%). To these reasons could be added cesareans induced either for a maternal, obstetrical, or fetal complication, such as eclampsia, lack of progress in labor, acute fetal distress, or elective cesarean section because some practitioners consider childbirth of patients with sickle cell disease as a risky situation both for herself and for the fetus [22]. In our context, elective cesarean section is performed in pregnant women at 36 weeks. It only occurred in 34 pregnant women (36%) whereas the emergency one occurred in 54 pregnant

women (57%).

Intrauterine growth restriction was observed in 49.7% of cases similar to the results of Nkwabong *et al.* in Cameroon [23]. Muganziyi *et al.* in Tanzania and Oppong *et al.* in Ghana found lower proportions with respectively 25.5% and 6.3% [5] [24]. In the general population, d'Almeida *et al.* [20] reported 13.4% of intrauterine growth restriction. According to Oteng Ntim *et al.* [15], homozygous sickle cell disease is associated with a risk of low birth weight, 4 times higher than in the general population. Pregnancy induces significant changes in patients with sickle cell disease such as increased metabolic needs, increased blood viscosity, and hypercoagulability, leading to an increased incidence of acute vaso-occlusive complications. This vaso-occlusion also occurs in the placenta, resulting in fibrosis, infarction, and villous necrosis, thereby causing impaired uteroplacental circulation and affecting the supply of nutrients to the growing fetus. The hypoxia and anemia observed in these pregnant women are also important factors that affect the growth of the fetus. Moreover, in low-income countries, other factors such as maternal malnutrition, and multiple pregnancies can contribute to that situation [8] [17] [25] [26]. In our study, 54.7% of neonates had a low birth weight, *i.e.* more than one in two neonates; which exposes them to increased mortality in the neonatal period and long-term metabolic and cardiovascular diseases.

Respiratory distress represented 40% of morbidities. Natu *et al.* [27] in India found 15.1% of respiratory distress and 4.12% in the general population by d'Almeida [20]. The frequency of respiratory distress is high in these neonates [8] [27]. It is the result of several factors including prematurity with all the respiratory complications it can induce: perinatal asphyxia and neonatal bacterial infection among others.

As for bacterial infection, it was observed in 30.5% of cases, similar to the results of Tsiba *et al.* in Congo Brazzaville [21]. d'Almeida *et al.* reported 25.6% of infection [20]. These neonatal infections are the consequence of maternal infections during pregnancy, especially those of the urinary tract. The main germs found in maternal urinary tract infections were *Escherechia coli* and *Klebsiella pneumoniae*, but in the neonate the diagnosis of infection was made on the basis of indirect biological signs because blood cultures were not available at the time of the study. And, the other bacteriological examinations did not allow isolation of a germ. These neonatals infections can also be explained by the poor follow-up of pregnancies in the pregnant women, which constitutes an obstacle to the early detection of maternal infections.

Perinatal asphyxia was also observed in 21.1% of cases in our work. Several authors have reported variable frequencies ranging between 6.7% and 34.6% [5] [8] [16] [22] [23]. Perinatal asphyxia is a frequent complication in these neonates. This is due to chronic fetal hypoxia, maternal and obstetrical complications such as infections, toxaemia of pregnancy, placenta previa, and severe anemia. As our study shows, most pregnant women had been admitted

to the maternity ward after a referral because of a maternal or fetal complication, which could explain a higher risk of asphyxia.

Other morbidities such as neonatal jaundice and anemia have also been described in the literature with a higher frequency in neonates with sickle cell disease [8] [27].

The live birth rate was 80% in our series, similar to that observed by Nwafor *et al.* [22] in Nigeria, showing that on average, one in five pregnancies does not result in delivery after 28 weeks and more in sickle cell pregnancy in our context.

Early neonatal mortality was at 8.4% in our study, similar to the rate reported by Silva Pinto in Brazil [28]. Nwafor *et al.* in Nigeria and Leborgne *et al.* in Guadeloupe found lower rates with respectively 3% and 4.4% [22] [29]. On the other hand, Nkwabong *et al.* in Cameroon and Tsiba *et al.* in Congo Brazzaville reported higher rates at 15.5% and 21.5% [21] [23]. In the general population, d'Almeida *et al.* found a rate of 7.2% [20]. Early neonatal mortality remains high in neonates of mothers with sickle cell disease. This mortality results from maternal and fetal complications noted during pregnancy, in particular intrauterine growth restriction, fetal asphyxia, and prematurity [7]. Perinatal asphyxia was the main cause of death of these neonates in 75% of cases. This cause has been found by several authors [8] [22] [23].

But in our study about one in two neonates was born prematurely and had intrauterine growth restriction. In general, neonates of mothers with sickle cell disease are more exposed to the risk of prematurity, intrauterine growth restriction, and high early neonatal mortality. These results are not influenced by geographical or economic factors, because the same data are reported in low and high-income countries [7]. These morbid states expose them to increased mortality due to all their complications.

In bivariate analysis, the factors associated with death were: parity ($p < 0.001$); mode of admission by referral to the maternity ward ($p < 0.004$), severity of maternal anemia ($p < 0.008$), birth weight less than 1500 g ($p < 0.002$), gestational age under 32 weeks ($p < 0.001$) and resuscitation duration greater than or equal to 5 minutes ($p = 0.001$). Indeed, multiparous mothers were 44 times more likely to have an early death of their neonate and primiparous mothers were 12 times more likely in our study. Similarly, those who had been referred from a peripheral health structure ran a greater risk of having an early death of their neonate as well as those with severe anemia. Neonates under 32 WA had 28 times more risk of death and those weighing less than 1500 g had fourteen times more risk of death. This is the consequence of complications related to very preterm neonates and low birth weight. Although there was no significant association between the place of pregnancy follow-up and early neonatal death, pregnant women who followed their pregnancy at the center for integrated medical care of infants and pregnant women with sickle cell disease (CPMINFED) had no neonatal death, demonstrating the importance of specialized follow-up. In multivariate analysis, resuscitation for at least five minutes was the main factor associated with death. Muganziyi *et al.* in Tanzania [5] observed a four times higher

risk of perinatal asphyxia in neonates of mothers with sickle cell disease resuscitated for more than five minutes compared to those without sickle cell disease. Perinatal asphyxia worsens the early neonatal prognosis in neonates of mothers with sickle cell disease.

5. Conclusion

More than one out of two neonates of mothers with sickle cell disease has a low birth weight. Early neonatal mortality is high with perinatal asphyxia as the main cause. It is important to revitalize the management policy for these pregnant women through early multidisciplinary follow-up to reduce these complications.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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