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Perinatal morbidity and mortality in neonates of mothers with sickle cell disease at the Teaching Hospital of Borgou /Alibori (Benin)-II

Abstract

Introduction: Pregnancy in women with sickle cell disease exposes the neonate to an increased risk of perinatal mortality.

Objective: To determine perinatal morbidity and mortality in neonates of mothers with sickle cell disease at the teaching hospital of Borgou/Alibori in northen Benin.

Patients and methods: This was a descriptive and observational study conducted in maternity and neonatology departments at the teaching hospital of Borgou/Alibori from January 1, 2015 to August 31, 2019. It included neonates of at least 22 weeks or weighing more than 500g, alive or not at birth from mothers with sickle cell disease. The variables studied were sociodemographic, clinical and evolutionary. 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.

Results: During the period, 130 pregnant women with sickle cell disease were admitted out of a total of 10,087, representing a frequency of 1.3%. The main perinatal morbidities were: acute fetal distress (10,4%), prematurity and intrauterine growth restriction (49.5%), respiratory distress (40%), bacterial infections (30.5%) and perinatal asphyxia (21.1%). Perinatal deaths occurred in 28 neonates and the perinatal mortality rate was 243.5‰.

Conclusion: Acute fetal distress and low birth weight are the main perinatal morbidities observed. Perinatal mortality in these neonates is higher than in the general population in our context. Hence the need for early multi-disciplinary care.

Keywords: morbidity, mortality, perinatal, neonates, mothers with sickle cell disease, Benin

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Introduction

Sickle cell disease is the most widespread genetic disease in the world with an average of 300,000 neonates affected each year.[1] It is a major public health and social problem with a high mortality before the age of five years in Sub-Saharan Africa.[2] Over the past four decades, significant medical advances in both low-income but mostly high-income countries have considerably improved the survival of affected people with the corollary of a substantial increase in the proportion of women of childbearing age.[3,4] But pregnancy in women with sickle cell disease is associated with a high risk of maternal, fetal and neonatal morbidity and mortality. Fetal and neonatal complications include, among others, intrauterine growth restriction (IUGR), acute fetal distress, premature delivery, and an increase in the perinatal mortality rate.[5,6] In sub-Saharan Africa where the management of these patients is still a real challenge, this risk is higher. The prevalence of maternal mortality among these pregnant women ranges from 0.38 to 1.29/100,000 births and the perinatal mortality rate ranges from 1.21 to 2.50/100,000 births.[7] The Republic of Benin, in West Africa, has a high prevalence of sickle cell disease. Although precise data on the incidence of pregnancies in women with this condition are not available, they are not by far as frequent because the prevalence of S trait carriers is approximately 25%.[7] A tiny number of these pregnant women have access to specialized care in the country. The Teaching Hospital of Borgou/Alibori at Parakou in northern Benin is a hospital where data on perinatal morbidity and mortality in neonates of these mothers are not known. In a previous study, we determined the early mortality and the factors associated in newborns born of mothers with sickle cell disease.[8] The objective of this work was to determine the perinatal morbidity and mortality in these neonates in order to help improve their management.

Patients and methods

This was a descriptive and observational study conducted in maternity and neonatology departments at the Teaching Hospital of Borgou/Alibori in Benin from January 1, 2015 to August 31, 2019.

Were included, any pregnant women with a major sickle cell syndrome (SS, SC, Sβ⁰-thal) meeting the following criteria:

- Whether or not she has followed her pregnancy at the maternity ward of the hospital.
- Having given birth at maternity ward of the hospital after 22 weeks and/or a neonate weighing at least 500g and/or having a length of at least 25cm.[9]
- Having a complete medical record for the pregnant woman includes: general information, medical history related to the sickle cell disease, gyneco-obstetrical history, information on the current pregnancy course, acute complications that occurred during pregnancy; information of 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 on the seventh completed day of life.

Excluded from the study, pregnant women with:

- incomplete medical records and those of their neonates
- Comorbidities: HIV infection, diabetes
- Spontaneous miscarriages during pregnancy and those who died during pregnancy

Pregnancy was considered well followed up when the pregnant woman had at least 8 quality prenatal consultations as recommended by WHO.[10] A stillborn child was defined as any child having shown no signs of life at birth from a pregnancy of at least 22 weeks and/or weighing at least 500 grams and/or having a length of at least 25cm at birth. Early neonatal death was defined as any death of a neonate alive at birth who died between 0 and 7 completed days of life. The stillbirth rate was the number of stillbirths per thousand total births. The early neonatal mortality rate was the number of early neonatal deaths per thousand live births. The perinatal mortality rate was defined as the number of stillbirths and early neonatal deaths per thousand total births.[8]

Sampling consisted of an exhaustive census of pregnant women meeting our inclusion criteria. The dependent variable was the existence of an early fetal or neonatal complication during pregnancy or at birth. The independent variables were sociodemographic, clinical and evolutionary in the fetus, the neonate and the mother. Data were collected from medical records, maternity and neonatology registers on the one hand and on the other hand using a direct structured interview with the pregnant women seen during the study. Data were entered and analyzed with Microsoft Excel 2013 software and Epi Info version 7.2. 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.

Results

Frequency of pregnant women with sickle cell disease

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 to the maternity ward of this hospital were recruited, representing a frequency of 1.3%. Among these pregnant women, 119 had usable medical records, but two pregnant women including a twin carrier had a spontaneous miscarriage and two others died during pregnancy. The study therefore involved 115 pregnant women (Figure 1).

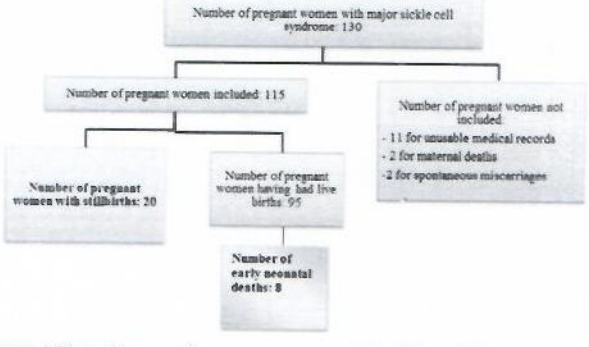

Figure 1 Flow diagram of pregnant women with sickle cell disease and their neonates.

Characteristics of pregnant women

The mean age of pregnant women was 25.81 ± 6.17 years with the extremes of 16 and 41 years. SC phenotype was the most represented (69.6%). There were no pregnant Sβ°-thal. Nulliparous women were predominant (49.6%). Pregnancies had been followed in a private practice (64.3%) and were referred from a peripheral health facility for an acute complication in 64% of cases as shown in Table 1.

Table 1 Distribution of pregnant women according to their socio-demographic characteristics, their past medical, surgical and obstetrical history (N=115)

	N	%
Age of mothers (years)		
<25	32	28
25-35	75	65
>35	8	7
Level of education		
None	47	41
Primary	25	21.7
Secondary	32	27.8
Higher	11	9.5
Phenotype		
SS	35	30.4
SC	80	69.6
Parity		
Nulliparous	57	49.6
Primiparous	28	24.3
Pauciparous	28	24.3
Multiparous	2	1.8
PNC		
< 8	15	87
≥ 8	100	13
Place of the pregnancy follow-up		
Private maternity	74	64.3
Maternity of Teaching Hospital	41	35.6
Mode of admission for delivery		
Referral	68	59.1
Direct to the maternity unit of hospital	47	40.9

Evolutionary characteristics of the current pregnancy

The pregnancy was not well followed up in 87% of cases (100/115). Table 2 shows the main maternal complications. The main maternal morbidities found were: vaso-occlusive crisis (78.3%), bacterial infections (45.2%) including 92% of urinary tract infection, severe anemia (26.1%) and severe malaria (27.8%).

Table 2 Distribution of pregnant women with sickle cell disease at CHUD-Borgou/Alibori according to their morbidities during pregnancy (N=115)

	N	%
Vaso-occlusive Crisis (VOC)	90	78.3
Bacterial infection	52	45.2
Severe malaria	32	27.8
Severe anemia	30	26.1
High Blood Pressure	12	10.4
Eclampsia	10	8.7

Perinatal morbidities

The evolution of pregnancy was made towards 20 stillbirths and 95 live births. The average gestational age of the stillborn neonates was 30.8 WA with the extremes of 22 and 39 WA. Stillbirths occurred between 28 and 36 WA in 75% of cases. The main fetal and neonatal morbidities reported are illustrated in Table 3. The main morbidities in

fetuses were: acute fetal distress (10.4%) with adnexal damage such as premature rupture of membranes (16.5%), and oligohydramnios (10.4%). Among live births, 89 were admitted to neonatology (93.6%). Delivery was by cesarean section in 89.5% of cases (85/95). It was an emergency cesarean section in 60% of cases (51/85). The average birth weight was 2474.316±530.15g with the extremes of 1100g and 3900g. The average birth length was 46.07 ± 4.18cm with the extremes of 27 and 52cm. It was a premature birth in 49.5% of cases dominated by preterm births (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. 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%). About 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.

Table 3 Distribution of perinatal morbidities observed in neonates of mothers with sickle cell disease at CHUD-Borgou/Alibori

	N	%
Fetal and adnexal morbidities (N= 115)		
Premature rupture of membranes	19	16.5
Acute fetal distress	12	10.4
Oligohydramnios	12	10.4
Threat of premature delivery	8	7
Placenta previa	1	0.8
Early neonatal morbidities (N=95)		
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

Perinatal mortality

A total of 28 perinatal deaths were recorded including 20 stillbirths and 8 early neonatal deaths for 95 live births in 115 pregnant women for whom the pregnancy resulted in a birth. The stillbirth rate was 174‰ (20/115). The early neonatal mortality rate was 84‰ (8/95). The average age of death in neonates was 11h with the extremes of 1h and 72h. The main cause of death was perinatal asphyxia in 75% of cases (6/8). These deceased neonates were premature in 75% of cases, 25% of them very preterm neonates. The perinatal mortality rate was 243.5‰ (28/115).

Discussion

Our study aimed to determine the perinatal morbidity and mortality in pregnant women with sickle cell disease. We have been able to describe the main maternal, fetal and early neonatal morbidities and determine the perinatal mortality rate. Given the retrospective nature of part of this work, we were unable to obtain a good data completeness on stillbirths. Gestational age was the main criterion used to evaluate the age of stillbirths more than the weight or length. Despite these limitations, our results remain valid.

It is well described that pregnancy and sickle cell disease have reciprocal influences on each other and that their association is a risky situation. The maternal and perinatal complications observed in our series are those conventionally reported in the literature.[7,11–13]

In this work, 1.3% of pregnant women had sickle cell disease. This frequency corroborates data in the literature in which approximately 0.6 to 1.4% of pregnant women suffer from sickle cell disease.[14,15] Several reasons could explain this relatively low frequency. In Sub-Saharan Africa, where the majority of patients are found, survival before the age of five can be fatal due to the limited access to specialized care.[2] Physiologically, women with sickle cell disease may have risk factors that may affect their ability to conceive, including chronic inflammation, oxidative stress, and ovarian sickling, which causes ischemia and reperfusion of the ovaries, can alter ovarian function and lead to a decrease in fertility in these patients.[13,16]

There is a predominance of double SC heterozygosity (68.9%) in our study. Rahimy in Cotonou and Traoré in Mali made the same observation.[7,17] This could be explained by the fact that heterozygotes SC have a better survival than homozygotes SS because they have a less severe phenotype and have a lower frequency of acute complications especially during the first years of life. As a result, they reach childbearing age more easily. However, they are exposed to a real risk at the end of their pregnancy. As they do not normally suffer from severe acute events, they may be less concerned about possible complications of pregnancy and this may result in poor follow-up of the preventive measures proposed during the prenatal period, as noted by some authors.[7]

The perinatal complications revealed by our results are not negligible. The main fetal morbidity was acute fetal distress (10.4%) with associated adnexal disorders such as premature rupture of membranes (16.5%), and oligohydramnios (10.4%). Alayed[18] reported a frequency of acute fetal distress at 18.5%. This fetal distress is the consequence of several factors including chronic fetal hypoxia, anemia and maternal infections, whether bacterial or parasitic due to malaria in our context. Premature rupture of membranes has been observed in 20% of cases. Wilson[15] in Ghana reported 13.5% of premature rupture of membranes in SS and 4.5% in SC phenotypes. As for oligohydramnios, Faye in Senegal,[19] found a frequency of 4.3% in their study. These fetal and adnexal disorders are classically described as frequent in pregnant women with sickle cell disease.[5,6,13,18]

As for early neonatal morbidities, they 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 were observed in our study, similar to the results of Ugboma in Nigeria and Costa in Brazil.[20,21] That is approximately one in two neonates. In the general population, d'Almeida[22] in the same hospital as ours, had reported 20.59% of prematurity in a study on perinatal morbidity and mortality. Our results are more than double those observed by this author in the general population. The incidence of prematurity is high in pregnant women with sickle cell disease with varying proportions depending on the studies between 11.8% and 75.4% in Sub-Saharan Africa.[18,23] Boafar in a meta-analysis reported that the risk of prematurity in these neonates was twice as high as in those of mothers without sickle cell disease.[12] The exact mechanism of this phenomenon is not clear, but an increased production of prostaglandin has been implicated.[13] The other reasons would be: anemia and maternal urinary tract infections as well as malaria, placenta previa and pregnancy toxemia, which are more frequently reported in these pregnant women. In this work, bacterial infections were observed in 45.2% of pregnant women with 92% of urinary tract infections, as well as gestational hypertension, its complications and severe maternal anemia. To these reasons could be added cesarean sections 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 the childbirth of patients with sickle cell disease as a risky situation both for herself and for the fetus.[24] In our context, the elective cesarean section is systematically performed in pregnant women with sickle cell disease at 36 WA. It only occurred in 34 pregnant women (36%) whereas the emergency one occurred in 54 pregnant women (57%).

Intrauterine growth restriction was reported in 49.7% of cases or approximately one in two neonates, similar to the results of Nkwabong in Cameroon.[24] Muganziyi in Tanzani and Oppong in Ghana found lower proportions with respectively 25.5% and 6.3%.[25,26] In the general population, d'Almeida[22] reported 13.4% of intrauterine growth restriction. According to Oteng Ntim,[27] homozygous sickle cell disease is associated with a risk of low birth weight, four times higher than in the general population. Pregnancy induces significant changes in patients with sickle cell disease leading to an increased incidence of acute vaso-occlusive complications. This vaso-occlusion also occurs in the placenta, resulting in fibrosis, and villous necrosis, thereby causing impaired utero placental circulation and affecting the supply of nutrients to the growing fetus. The hypoxia and anemia observed in these pregnant women would also be important factors that affect the growth of the fetus. Moreover, in low-income countries, like ours other factors such as maternal malnutrition, multiple pregnancies can contribute to that situation.[13,20,28] In our study, 54.7% of neonate had a low birth weight, i.e. more than one in two neonates which exposes them to an increased mortality in the neonatal period and to long-term metabolic and cardiovascular diseases.

Respiratory distress represented 40% of morbidities. Natu[29] in India noted 15.1% of respiratory distress and 4.12% in the general population by d'Almeida.[22] The frequency of respiratory distress is high in these neonates.[13,29] 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 in Congo Brazzaville.[23] These neonatal infections are the consequence of maternal infections during pregnancy, especially those of the urinary tract. They can also be explained by the poor follow-up of pregnancies in these women; which constitutes an obstacle to the early detection of maternal infections.

Perinatal asphyxia was also involved in 21.1% of cases in our work. Several authors have reported variable frequencies ranging between 6.7% and 34.6%.[13,19,24,25] Perinatal asphyxia is a frequent complication in these neonates. This is due to chronic fetal hypoxia, maternal and obstetrical complications such as infections, toxemia of pregnancy, placenta previa and severe anemia. As our study shows, most pregnant women had been admitted to the maternity ward after a referral due to 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 of mothers with sickle cell disease.[13,29]

Perinatal mortality in our series was around 243.5‰. Authors in Sub-Saharan Africa noted higher rates of 266‰, particularly in Cameroon,[24] whereas in Ghana, Oppong and Asare reported lower rates of 74‰ and 23‰ respectively.[26,11] Stillbirths contribute heavily to these results with a stillbirth rate of 174‰ in our study. Like perinatal mortality rates, stillbirth rates are variable from studies and constitute the burden of perinatal mortality in these pregnant women. On the other hand, authors in Brazil[20,30] reported lower stillbirths rates of 17‰ and 2.71‰ respectively. These low rates would be due to intensive follow-up of pregnant women. In the study carried out in the general population,[22] the minimum reference gestational age for stillbirths was 22 WA. The stillbirth rate noted in our work is double that reported in this study in the general population, testifying to the high risk of fetal mortality in these pregnant women. These differences observed in the studies could also be explained by the limit defined in terms of gestational age with regard to stillbirths. According to many authors, the limit used was ≥8WA.[7,15,17,30] The risk of stillbirth is higher in pregnant women with sickle cell disease,[12–15,19] and these stillbirth rates, although variable depending on the country, remain high especially in countries with limited resources. Beyond the environmental and socio-economic factors, in term of physiology, pregnancy induces significant changes described above, causing chronic hypoxia and an unfavorable fetal prognosis.[13] Chronic anemia in these pregnant women increases the risk of stillbirth.[15]

Early neonatal mortality was at 84‰ in our study, similar to the rate reported by Silva Pinto in Brazil.[31] In the general population d'Almeida found a rate of 72.5‰.[22] The early neonatal mortality remains high in neonates of mothers with sickle cell disease. This mortality results from maternal and fetal complications reported during pregnancy, in particular intrauterine growth restriction, fetal distress and spontaneous or induced prematurity.[12] Perinatal asphyxia was the main cause of these neonates death (75%). This cause has been found by several authors.[13,24,25]

Overall, perinatal mortality in our study is high. The lower mortality rates mentioned above and observed in Ghanaian study,[11,26] were obtained during studies carried out as part of a multidisciplinary management implementation combining gynecologists, hematologists and pediatricians. In the study of Asare,[11] the perinatal mortality rate fell from 60.8‰ before the multidisciplinary approach to 23‰ after that, comparable to those of developed countries such as United Kingdom.[32] Although the reasons for this decline in perinatal mortality are unclear, according to the author, the increase in the live birth rate would include: a reduction in maternal mortality, series of third trimester ultrasound scans to assess the fetal growth and well-being, umbilical artery Doppler studies for intrauterine growth, and rigorous follow-up of mothers and fetuses during labor. Such care approaches experienced in sub-Saharan Africa could be implemented in our context to improve the perinatal prognosis of these neonates.

Conclusion

Perinatal morbidities in neonates of mothers with sickle cell disease in our context are dominated by acute fetal distress and low birth weight. Moreover, perinatal mortality remains highland stillbirth contributes to worsen the prognosis. Early multidisciplinary care would help improve this prognosis.

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Conflicts of interest

No conflict of interest exists.

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