Performance of Sickle SCAN® in the Screening of Sickle Cell Disease in Kisangani Pregnant Women and Attitude towards Results

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Abstract

In the Democratic Republic of the Congo, the sickle cell trait carriage is estimated at 25%. Routine neonatal screening is not a common practice, leading to a very late diagnosis. In this study, the screening of pregnant women was assessed as well as their attitudes. This is an analytical cross-sectional study conducted in 245 pregnant women, sampled by convenience in four hospitals in Kisangani city (Democratic Republic of Congo) and screened using the sickle SCAN® test, from February 1 to July 31, 2019. The sensitivity and specificity of the latter were determined using liquid chromatography coupled with mass spectrometry as the gold standard. The attitudes of 240 pregnant women without previous screening history were assessed upon the announcement of the results. The sensitivity of screening for hemoglobin (Hb) AA and Hb AS was 96.69% and 98.39%, respectively; while the specificities were 99.43% and 96.32%, respectively. The Kappa coefficient (κ) was excellent. Concerning attitudes, Hb SS pregnant women and 55.17% of AS pregnant women worried when the results relating to their hemoglobin status were announced. The sickle SCAN® test was found reliable for sickle cell disease screening in Kisangani. The announcement of the results, mainly positive, raises worry among pregnant woman. Therefore, we recommend the involvement of a clinician psychologist for pre-screening counselling and for results announcement, as well as early newborns and unmarried teenage girls screening.

Keywords

Sickle SCAN®, Liquid Chromatography, Pregnant Women, Attitudes, Kisangani

1. Introduction

As indicated by the World Health Organization (WHO) in its 2008 report, hemoglobin disorders are a significant health problem in 71% of the world's 229 countries. They also account for 89 per cent of the world's birth rate [1].

Every year, an estimated 400,000 babies are born with SCD worldwide [2]. According to the global hemoglobinopathy epidemiology database, approximately 7% of pregnant women are carriers of hemoglobinopathies; more than 9 million carriers of the sickle cell trait (SCT) HbAS women become pregnant each year; and there are approximately 948,000 new couples with SCD risk (1% of couples) and more than 1.7 million pregnancies in carrier couples. The SCD risk of their partner also being carriers ranges from 0.1% to 40% (with an average of 14%) [1].

In Africa, the high prevalence of SCT makes it a public health concern. This prevalence varies by region, from 10% to 40% in equatorial Africa, from 15% to 30% in western Africa [3].

In the Democratic Republic of Congo (DRC), the prevalence of SCT is estimated at 25%. In the neonatal period, 2% of newborns are homozygous sickle cell carriers and about 40,000 births of sickle cell newborns are estimated each year [4]. In Kisangani, a study conducted by Batina *et al.* [5] reported a prevalence of 23.3% sickle cell trait carriers among newborns.

The complications of SCD are at the root of frequent hospitalizations and multiple stigmatization, and difficulties in social and school integration for seek children [6]. According to the results of studies conducted by Mbiya *et al.* [6] and Luboya *et al.* [7], parents of sickle-cell children interviewed about their daily life stated that the disease modifies the family atmosphere. Questions and worries about the child's future raise family tensions, and consequently affect the couple's quality of life. Among the social repercussions of sickle cell disease in the DRC, permanent stress is the most frequently reported; it is followed by divorce [7].

Thus, to prevent risk in children, screening for sickle cell trait and beta-thalassemia is recommended before marriage to prevent marriage at risk through genetic counselling [8]. WHO believes that screening for hemoglobinopathies should be part of the basic health services in most countries. Carriers and at-risk couples need to be informed about the dangers they face and how to reduce them [1].

However, for many reasons, in the majority of countries in Sub-Saharan Africa (SSA), including the DRC, screening for SCD is not always part of premarital

examinations, which are not systematic. In these countries, the basic means for its management have remained insufficient, systematic neonatal screening for the disease is not common practice and diagnosis is generally made late [9] [10].

In these regions, the majority of screenings for sickle-cell anemia are either expensive or not available in hospitals. These include isoelectrofocusing (IEF), high-performance liquid chromatography (HPLC) and capillary electrophoresis (CE) etc. In addition, these techniques mostly expensive require permanent and stable electric current and specialized analysts who are not always available. All these situations contribute to the delay in the result delivery thus to difficult in reaching and informing children and families particularly for those who test positive [11].

The socio-cultural consideration to this disease in Africa constitutes an additional obstacle to the screening: SCD is subject to numerous taboos and stigma, ranging from isolation and abuse of the patient to parental divorce [6] [12].

In order to overcome the financial and technical problems encountered mainly in countries with limited resources, WHO and the National Institute of Health in the United States of America (USA) had, in 2016, called for the development of diagnostic methods that have to be simple, reliable, accurate and affordable [13] [14].

Since then, rapid diagnostic tests (RDTs) for SCD such as sickle SCAN® have been developed and some studies have been initiated to test their performance *i.e.*, the one conducted in the USA in 2016 [11], the screening for sickle-cell anemia done in Nigeria [15], in Togo and in Mali [16], as well as in France [17] from 2017 to 2018 and targeting either newborns, infants over 6 months of age or adults in general.

These very encouraging results motivated us to evaluate the sickle SCAN® test among pregnant women at Kisangani city while evaluating their attitude towards release of the results. Indeed, women are often socio-family victims who bear the brunt of the chronic diseases consequences and more particularly sickle cell anemia. On the other side, the high prevalence of SCT in Kisangani contrasts with the inadequacy of available diagnostic tests such as the Emmel test that is qualitative and does not distinguish between homozygotes and heterozygotes, the electrophoresis that is conditioned by the recording of at least 20 samples to save reagents.

In view of the above, we conducted this study in order to access the performance of sickle SCAN in the diagnosis of SCD in pregnant women in Kisangani and to determine the reaction of pregnant women screened.

2. Material and Methods

2.1. Study Design, Setting and Period

This is an analytical cross-sectional study, conducted in 4 hospitals in the city of Kisangani namely: the Promotion Santé de la Femme (PSF) medical center; the General Referral Makiso's Hospital, the General Referral Kabondo's Hospital,

and the Kisangani University Clinics (CUKIS), from February 1st to July 31st 2019. The choice of the CUKIS and the PSF was motivated by the presence of the medical staff specialists, allowing us to minimize loss of cases. The two general referral hospitals were chosen because of a high rate of pregnant women attendance.

2.2. Sampling among Women

As shown in the flowchart in Figure 1, our sample consisted of 245 pregnant women of 14 - 43 years old, selected by convenience. These pregnant women had not a history of transfusion for at least three months, their pregnancy was at least 28 weeks of amenorrhea, they had full information and they gave their informed consent to be included in the study.

2.3. Data Collection of Blood and Screening

1) Data collection

Data collection was prospective. Data were collected after the ANC and they were recorded in the data collection sheet. Before starting the data collection, investigators were trained in using the SCD kit and in the technique of collecting samples on blotting paper.

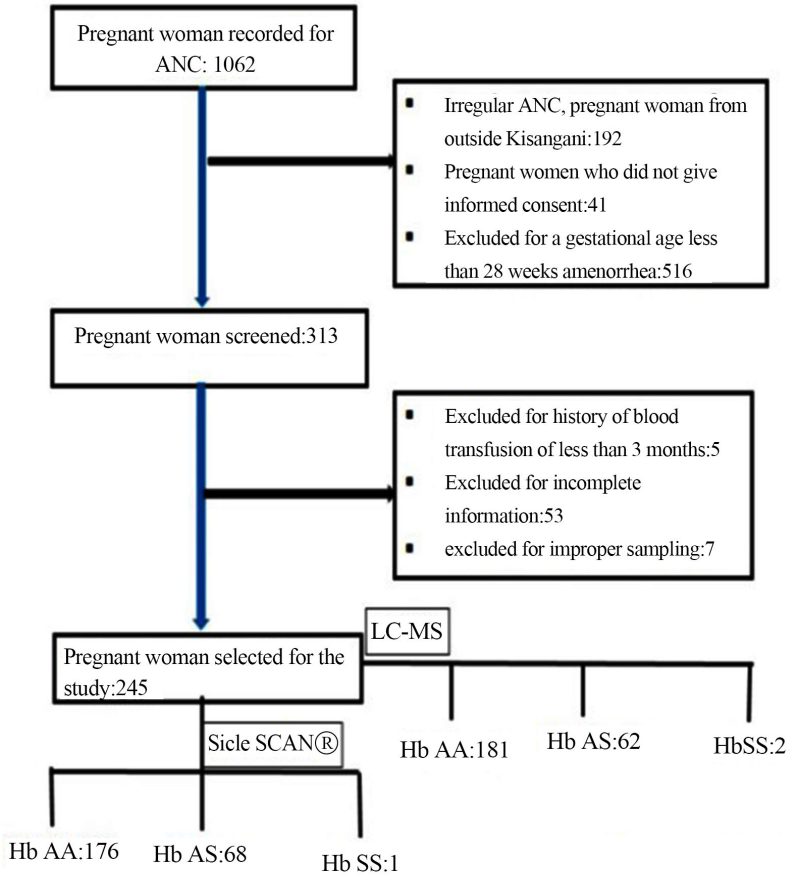

Figure 1. Recruitment of the respondents.

After ANC, the investigators obtained the informed consent of pregnant women. Using a standardized questionnaire, they collected informations related to the socio-demographic parameters of pregnant women, such as age, education level, profession, marital status, commune of residence; their gynecological and obstetric history; history of a previous screening and their socio-economic level. In order to determine the socio-economic level of our respondents, we refer to the household economic well-being index as constructed by Tchamda and Nkabkob [18]. This index takes into account some households' durable assets and housing characteristics. For our study, in relation to household durable assets, we looked for whether or not households owned: television, radio, vehicle and refrigerator, and mobile phone; and in relation to housing characteristics, we investigated the availability of electricity, the supply of drinking water, the use of modern toilets, the construction of walls made of durable materials, and the use of embers or stoves as fuel for cooking. We first assigned a score to each of the durable assets or characteristics of the dwelling house: one for the answer "yes" and zero for the answer "no". Next, we assigned a total score for each household corresponding to the sum of all the scores obtained for each good or characteristic of the dwelling house. Thus, households were ranked in ascending order of total score and divided into 5 categories called quintiles: poorest (total score = 1 - 2), second or poor (total score = 3 - 4), middle (total score = 5 - 6), fourth or rich (total score = 7 - 8) and richest (total score = 9 - 10).

After interviewing pregnant women, the investigators screened them. Hemoglobin status screening in Kisangani was performed using the sickle SCAN® device while diagnostic confirmation was performed using the LC-MS at the University Hospital of Liege in Belgium. Mass spectrometry is a reference method that has been found to be more sensitive and more specific than IEF and HPLC-UV [19].

To guarantee confidentiality, each respondent was given a unique number, which was recorded on the sickle scan disc and the corresponding blotting paper.

We have used the Sickle SCAN®, manufactured by the BioMedomics (Research Triangle Park, NC, USA). After the collecting of 5 µl of blood for sickle scan screening, a second sample of 2 drops of blood was collected and placed on the blotting paper (CMC C/Horacio Lengo, Malaga, Spain), used by the laboratory of genetic biochemistry of the University Hospital of Liege. The blotting paper was air-dried for at least 1 hour before storage in a paper envelope prior to transfer abroad.

The results of the sickle scan screening were read by the physician of the investigative team who scheduled the follow-up ANC visit for the definitive results. Immediately after the reading, all data forms were collected, sickle scan discs and blotting paper used. The dried blood samples on blotting paper were sent to the laboratory of genetic biochemistry at University Hospital of Liege for examination using LC-MS. The LC-MS results were returned to the investigators

by e-mail. The latter announced results to the pregnant women and observed their attitudes when those women came for the follow-up ANC checkup.

The attitudes upon to announcement of Hb status results concerned only pregnant women with no previous screening history. Three types of reactions were observed: satisfaction, indifference and worry.

2) Kit operating principle

Sickle SCAN® is known as a rapid, qualitative lateral flow immunoassay test for the identification of sickle cell disorder of hemoglobins A, S, and C. The test is made up of three indicators which detect the presence of those hemoglobins, allowing the user to rapidly distinguish between normal, carrier, and sickle cell samples. Five microliters of blood taken by fingerpick, heelstick, or venipuncture using the provided Capillary Sampler is placed into the buffered loaded pretreatment module to release hemoglobin by lysing erythrocytes. Three drops of the treated sample are dropped from the pretreatment Module and added to the sample inlet of the sickle SCAN® cartridge. The sample will interact with antibody conjugated colorimetric detector nanoparticles and travel to the capture zone. Results can be read within five minutes. The presence of hemoglobin variants A, S, and C will be indicated by blue lines in their designated regions as can be shown in **Figure 2** [20].

3) Data analysis

The data were encoded using Excel 2013 and processed using the EPI Info7 software. For the Sample Description, we calculated frequency and percentage. Sensitivity and specificity of the sickle scan for Hb AA, AS and SS were manually calculated, according to the following formulas:

$$\text{Sensitivity} = \frac{\text{True positive}}{\text{True positive} + \text{False negative}}$$

$$\text{Specificity} = \frac{\text{True negative}}{\text{True negative} + \text{False positive}}$$

LC-MS was considered as the gold standard.

The results of the sickle SCAN® and LC-MS screening were compared by calculating the percent agreement (Cc) and the Kappa coefficient (κ). In medicine, a correct κ coefficient between two techniques must be greater than 0.8 [21].

Figure 2. Monitoring of the test Hb results using Sickle SCAN®. Legend: Form left to right: Hb AA, Hb As, HbAS (with S pale), and Hb SS.

The κ has been calculated using the following formula:

$$\kappa = \frac{Cc - Ca}{1 - Ca}$$

where

$$Cc = \frac{\text{Number of matching agreement}}{\text{number of compared agreements}};$$

and,

Expected agreement (Ca) =t1n1 + t2n2 + t3n3/N2.

Agreement was considered insufficient if κ is between 0 and 0.40, satisfactory if κ is between 0.40 and 0.75, excellent if κ is greater than 0.75. A κ less than 0 indicates disagreement [22].

3. Results

3.1. Description of Respondents

The socio-demographic characteristics of the respondents are presented in Table 1.

Table 1. The socio-demographic characteristics of surveyed pregnant women.

Parameter	HbAA Pregnant women N = 181	HbAS Pregnant women N = 62	HbSS Pregnant women N = 2	Total N = 245 (%)
	Frequency (%)	Frequency (%)	Frequency (%)	
Age (years) (median = 27)				
≤18	23 (12.71)	5 (8.06)	0 (0.00)	28 (11.43)
19 - 34	119 (65.75)	45 (72.58)	1 (50.00)	165 (67.35)
≥35	39 (21.55)	12 (19.35)	1 (50.00)	52 (21.22)
Parity				
1	52 (28.73)	17 (27.42)	0 (0.00)	69 (28.16)
2	30 (16.57)	14 (22.58)	1 (50.00)	45 (18.37)
≥3	99 (54.70)	31 (50.00)	1 (50.00)	131 (53.47)
Level of education				
Primary	24 (13.26)	8 (12.90)	0 (0.00)	32 (13.06)
Secondary	112 (61.88)	35 (56.45)	2 (100.00)	149 (60.82)
Higher and University	45 (24.86)	19 (30.65)	0 (0.00)	64 (26.12)
Socio-economic level				
Poorest	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Poor	9 (4.97)	4 (6.48)	0 (0.00)	13 (5.31)
Middle	118 (65.19)	37 (59.68)	1 (50.00)	156 (63.67)
Rich	44 (24.31)	13 (20.97)	1 (50.00)	58 (23.67)
Richest	10 (5.52)	8 (12.9)	0 (0.00)	18 (7.35)
Profession				
Pupil/Student	18 (9.94)	7 (11.29)	0 (0.00)	25 (10.20)
Unwaged	116 (64.09)	39 (62.90)	2 (100.00)	157 (64.08)
Waged	47 (25.97)	16 (25.81)	0 (0.00)	63 (25.71)
Marital status				
Single	16 (8.84)	11 (17.74)	0 (0.00)	27 (11.02)
Married	165 (91.16)	51 (82.68)	2 (100.00)	218 (88.98)
Previous screening				
Yes	0 (0.00)	4 (6.45)	1 (50.00)	5 (2.04)
No	181 (100.00)	58 (93.55)	1 (50.00)	240 (97.96)

Table 1 indicates that the age of the surveyed pregnant women ranged from 14 to 43 years (median age at 27 years). 67.35% of the pregnant women surveyed were between 19 and 34 years. More than half, 53.47% were multiparous, 60.82% had secondary school education level, 64.08% were unwaged and 63.67% had a middle socio-economic level. In addition, 88.98% of pregnant women lived as couples and 97.96% were unaware of their Hb status prior to participate in our study.

3.2. Results of Sickle SCAN® and Agreement with LC-MS

In HbAS pregnant women the HbS band appeared earlier than the HbA band, which appeared last. From left to right, Figure 2 shows the results to HbAA, HbAS, HbAS and HbSS. We noticed a pale S line in the Hb AS that can possibly lead to confusing with HbAA.

Table 2 shows the agreement between the results of the sickle scan and those of the LC-MS. It also provides information on the sensitivity and specificity of the sickle SCAN® in relation to the screening of different hemoglobin statuses.

While reading Table 2, we can see that there was an excellent agreement between sickle SCAN® and LC-MS results for 237 out of 245. Indeed, the sickle SCAN® sensitivities for HbAS was 98.39% while the specificity was calculated to be 96.32%; and 99.59% for HbSS.

3.3. Attitudes of Screened Pregnant Women upon the Announcement of LC-MS Results

Table 3 presents the reactions to the announcement of the definitive diagnosis made by LC-MS analysis of dried blotting paper samples. Pregnant women who were relieved and/or happy to know their hemoglobin status was considered satisfied. Some of them asked that their husbands and children be screened as well.

The pregnant women who expressed disinterest when the results were announced were considered indifferent; they did not ask any questions of understanding and the majority of them stated that the screening was not worth the effort and that there had never been any SCD patients in their families.

Table 2. Agreement of sickle SCAN® and LC-MS results.

		LC-MS Result		Performance of Sickle SCAN®		
		AA n (%)	AS n (%)	SS n (%)	Sensibility	Specificity
Sickle	AA n (%)	175 (96.69)	1 (1.62)	0 (0.00)	96.69%	99.43%
SCAN®	AS n (%)	6 (3.31)	61 (98.39)	1 (50.00)	98.39%	96.32%
Results	SS n (%)	0 (0.00)	0 (0. 00)	1 (50,00)	50.00%	99.59%

Table 3. Attitude of screened pregnant women upon the announcement of results.

	Indifference n (%)	Worry n (%)	Satisfaction n (%)	Total (%)
AA	35 (19.34)	0 (0.00)	146 (80.66)	181 (75.41)
AS	19 (32.76)	32 (55.17)	7 (12.07)	58 (24.16)
SS	0 (0.00)	1 (100.00)	0 (0.00)	1 (0.42)
Total	**54 (22.50)**	**33 (13.75)**	**153 (63.75)**	**240 (100.00)**

The ones who worried were those who were anxious and panicked. On the one hand, this was expressed by multiple questions asked to rule out complications related to their status and its negative implications for their offspring, and on the other hand, some of them cried when the results were announced. Their attitudes needed further explanation for a better understanding.

Analysis of **Table 3** shows that 55.17% of AS pregnant women worried when the result was announced and 100.00% of SS pregnant women worried.

4. Discussion

The results of this first preliminary study of pregnant women in Kisangani showed an excellent sensitivity and specificity of the sickle SCAN® test compared to the LC-MS for HbAA and HBAS.

The calculated κ coefficient showed an excellent agreement between the two tests. However, for HbSS, the sample was too low to evaluate the two parameters. One blood sample was screened and confirmed HbSS whereas the other presented doubt of HbSS in the screening and confirmation. Based on its medical history and the medical consultation, one can confirm HbSS status of the second pregnant woman. However, the staff could not collect much blood volume as for other.

Except this unexpected situation, specificity and sensitivity were closer to the values of other studies.

In the USA, Kanter *et al.* [23] found a sensitivity and specificity of 99% when they compared the sickle SCAN® with HPLC in the diagnosis of Hb AC, SC, AS, SS and AA. In the same country, McGann *et al.* [2] compared the sickle SCAN® with capillary electrophoresis. It showed a sensitivity of 98.3% to 100.0% higher than what we found; and a specificity of 92.5% to 100.0% similar to ours. The test demonstrated a sensitivity of 98.4% and a specificity of 98.6% for the diagnosis of Hb SS, while the sensitivity as well as the specificity for the diagnosis of Hb SC was 100.0%.

In its preliminary study conducted in Nigeria, Nwegbu *et al.* [15] found sensitivity, specificity and efficacy of 100.0%, 98.2% and 98.2%, respectively, for Hb SS and Hb SC screening by sickle scan compared to HPLC as the standard method. The study conducted by Segbene *et al.* [16] in Lomé in which sickle SCAN® was compared to capillary electrophoresis found a sensitivity and specificity of 100.0% for the detection of HbAA and HbCC. The specificities were 97.7%; 97.6%; 95.6% and 94.9% respectively for Hbs SC, SS, AS and AC. While in Bamako the sensitivity and specificity was 100.0% for all phenotypes with HPLC as the standard method [16]. A prospective study conducted in Tanzania assessed the performance of sickle SCAN® compared to capillary electrophoresis. With inexperienced medical personnel, the sensitivity and specificity were 98.1% (95% CI 95.9% - 99.3%) and 91.1% (95% CI 87.5 - 94.0) respectively. In experienced users, sensitivity and specificity were 99.4% [24].

The high specificity observed in the various studies mentioned may reflect the

ability of the test to exclude other types of hemoglobin when diagnosing different varieties of Hb (AA, AS, and SS) in different environments.

The excellent agreement of the results obtained in our study is similar to those found by McGann *et al.* [2] who found a κ-coefficient of 0.93 (z 533. 1, $p < 0.0001$); and Khoa *et al.* [17] who found a 96% agreement between the Sickle SCAN® and HPLC results. In the four cases of disagreement in the sample of Khoa *et al.*, the anti-HbS antibody cross-reacted with HbE (n = 2), HbD (n = 1) or HbX (n = 1). The study also noted that HbA and HbS were always detected when present at levels greater than 1% and 2%, respectively.

In addition, Steele *et al.* [25] evaluated an alternative diagnostic method for S and C hemoglobinopathies, the SC Hemotype on 587 samples from the USA, Ghana and Martinique. HemoTypeSC had an overall sensitivity of 99.5% and specificity of 99.9% across all hemoglobin phenotypes. The test had 100% sensitivity and specificity for sickle cell anemia. Sensitivity and specificity for detection of normal and trait states were >99%.

With regard to the attitudes shown by the pregnant women when the results were announced, we noted that the announcement of HbSS status always caused worry; whereas the announcement of AS status caused worry of variable expression in 55.17% of the pregnant women surveyed.

We did not have access to studies on the reaction of individuals with AS or SS screening. Nevertheless, a few authors have conducted research among parents and families of SCD patients. According to Luboya *et al.* [6] the announcement of the disease plunges parents into permanent anxiety and worry; anxiety due to the fact that the disease is chronic and lethal in low-resource settings such as the DRC. The anxiety is caused by the fact that they imagine their child suffering for the rest of his/her life. The feeling of panic is due to the image of SCD portrayed in sub-Saharan societies; that of a shameful disease, associated with the curse and of which unique evolution leads to the death of the child. The results of a survey conducted in Cameroon had revealed that in families, women experienced SCD diagnosed in their children as a "curse" or an inability to give birth to healthy children [26].

Like Luboya et *al.* [6] we believe that the majority of those respondents had sufficient knowledge about SCD and its consequences, especially in social terms. This explains the fact that they displayed a feeling of panic. Women particularly think that the diagnosis of the disease could end their marriage if other family members were informed.

For other studies, the parents' panic reaction to the announcement of the disease is more related to the lack of knowledge about SCD. The denial of the disease and the parents silence testify of the devaluing image of SCD in African society [27] [28] [29].

Our study is the first to screen pregnant women for SCD in the eastern region of the DRC. It is also one of the first studies to highlight the negative psychological impact that the announcement of the result can have on a pregnant woman with HbAS and HbSS who is unaware of it.

The significance of this study lies in the fact that the determination of the specificity of the sickle scan and its excellent agreement with the LC-MS has led to the conclusion that this test is reliable in Kisangani. Therefore, screening for SCD in pregnant women will become easy in this city. It shows the need for good psychological support during screening for SCD in order to reduce cases of panic.

Our study had some limitations. First, the sample size was low and it included only two SS pregnant women. Second, we did not determine the fraction of different types of Hb in AS pregnant women. Third, partners and children of pregnant women were not screened; that why the percentage of couples with risk was not calculated.

5. Conclusion

The sickle SCAN® was found reliable for the screening of SCD in Kisangani, where hospital laboratories are poorly equipped, with a performance close to LC-MS. The announcement of the results had created worry among most AS and SS pregnant women who were unaware of their hemoglobin status. Based on the rapidity and reliability of the results, screening for SCD in pregnant women will become easy in this city. We expect to perform the mass screening of SCD focusing on newborns and young unmarried adolescents mass screening, and recommend the presence of a clinician psychologist for the results announcement.

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Contribution of the Authors

YNU: designed the study, supervised the screening and drafted the article.

JJS: made substantial contribution to the study design, analysis and interpretation of data.

RMD: supervised the overall study, revised the article critically for important intellectual content.

GKB: checked the consistency of the results in relation to the research problem.

HTA: made the statistical analyses and checked their consistency.

SLe: perform the LC-MS analyses at Liege.

FBo: check the consistency of the LC-MS test results and of the Sickle SCAN® as well.

SBA: made the substantial contribution to the concept of the entire work.

Ethical Considerations

The study was approved by the University of Kisangani Ethics Committee (Ref CER/006/GEAK/2019). All respondents gave their informed consent to participate in the study.

Conflicts of Interest

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

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