Profile of Reproductive Issues Associated with Different Sickle Cell Disease Genotypes

Perfil reprodutivo associado aos diferentes genótipos da doença falciforme

Flávia Anchielle Carvalho[1,2] Ariani Impieri Souza[1,2] Ana Laura Carneiro Gomes Ferreira[1] Simone da Silva Neto[2] Ana Carolina Pessoa de Lima Oliveira[2] Maria Luiza Rodrigues Pinheiro Gomes[2] Manuela Freire Hazin Costa[1,3]

[1] Instituto de Medicina Integral Prof. Fernando Figueira (IMIP), Recife, PE, Brazil
[2] Faculdade Pernambucana de Saúde (FPS), Recife, PE, Brazil
[3] Universidade Federal de Pernambuco (UFPE), Recife, PE, Brazil

Address for correspondence Ariani Impieri Souza, PhD, Instituto de Medicina Integral Prof. Fernando Figueira (IMIP), Rua dos Coelhos, 300 Boa Vista, 50070-550–Recife, PE, Brazil (e-mail: ariani@imip.org.br).

Rev Bras Ginecol Obstet 2017;39:397–402.

Abstract

Purpose To describe the reproductive variables associated with different sickle cell disease (SCD) genotypes and the influence of contraceptive methods on acute painful episodes among the women with the homozygous hemoglobin S (HbSS) genotype.

Methods A cross-sectional study was conducted between September of 2015 and April of 2016 on 158 women afflicted with SCD admitted to a hematology center in the Northeast of Brazil. The reproduction-associated variables of different SCD genotypes were assessed using the analysis of variance (ANOVA) test to compare means, and the Kruskal-Wallis test to compare medians. The association between the contraceptive method and the acute painful episodes was evaluated by the Chi-square test.

Results The mean age of women with SCD was 28.3 years and 86.6% were mixed or of African-American ethnicity. With respect to the genotypes, 134 women (84.8%) had HbSS genotype, 12 women (7.6%) had hemoglobin SC (HbSC) disease genotype, and 12 (7.6%) were identified with hemoglobinopathy S-beta (S-β) thalassemia. The mean age of HbSS diagnosis was lower than that of HbSC disease, the less severe form of SCD ($p < 0.001$). The mean age of menarche was 14.8 $\pm$ 1.8 years for HbSS and 12.7 $\pm$ 1.5 years for HbSC ($p < 0.001$). Among women with HbSS who used progestin-only contraception, 16.6% had more than 4 acute painful episodes per year. There was no statistically significant difference when compared with other contraceptive methods.

Conclusion With respect to reproduction-associated variables, only the age of the menarche showed delay in HbSS when compared with HbSC. The contraceptive method used was not associated with the frequency of acute painful episodes among the HbSS women.

Keywords
- sickle cell disease
- sickle cell anemia
- menarche
- contraception

received
January 16, 2017
accepted
April 25, 2017
published online
July 6, 2017

DOI https://doi.org/10.1055/s-0037-1604179.
ISSN 0100-7203.

Resumo

Objetivo Descrever as variáveis reprodutivas em diferentes genótipos da doença falciforme (DF) e a influência dos métodos contraceptivos na frequência das crises álgicas em mulheres com homozigose da hemoglobina S (HbSS).

Métodos Estudo de corte transversal realizado entre setembro de 2015 e abril de 2016 com 158 mulheres com DF atendidas em um centro de hematologia no Nordeste do Brasil. As variáveis reprodutivas dos diferentes genótipos da DF foram avaliadas utilizando-se o teste de análise de variância (ANOVA) para comparação de médias e o teste de Kruskal-Wallis para comparação de medianas. A associação entre o método contraceptivo e a frequência das crises álgicas foi avaliada pelo teste Qui-quadrado.

Resultados A idade média das mulheres com DF foi de 28,3 anos e 86,6% eram afrodescentes. Em relação aos genótipos, 134 mulheres (84,8%) tinham genótipo HbSS, 12 mulheres (7,6%) tinham genótipo para doença da hemoglobina SC (HbSC) e 12 (7,6%) foram identificadas com beta talassemia (S-β). A idade média do diagnóstico de HbSS foi menor do que a da HbSC, sendo esta a forma menos grave da DF ($p < 0,001$). A idade média da menarca foi de 14,8 ± 1,8 anos para HbSS e de 12,7 ± 1,5 anos para HbSC ($p < 0,001$). Entre as mulheres com HbSS que fizeram contracepção com progesterona isolada, 16,6% apresentaram mais de 4 episódios de crises álgicas agudas por ano. Não houve diferença estatisticamente significativa quando comparado com outros métodos anticoncepcionais.

Conclusão Em relação às variáveis reprodutivas, apenas a idade da menarca apresentou atraso no HbSS em relação ao HbSC. O método anticoncepcional utilizado não foi associado à frequência de crises álgicas entre as mulheres com HbSS.

Palavras-Chave

- doença falciforme
- anemia falciforme
- menarca
- anticoncepção

Introduction

Sickle cell disease (SCD) includes any hemoglobinopathy in which the sickle mutation is inherited, such as homozygosity for hemoglobin S (HbSS, sickle cell anemia) and heterozygosity for hemoglobin S (HbS) with other hemoglobin anomalies, resulting in: hemoglobin SC disease (HbSC), hemoglobin SD disease, hemoglobinopathy S-α-thalassemia (Sα-thalassemia), hemoglobinopathy S-β-thalassemia (Sβ-thalassemia), and other less commons SCD genotypes. The disease course depends in part on the SCD genotype; HbSS tends to result in the most severe form of the disease, while a more benign course may occur with HbSC, although adverse events have been observed in all genotypes.[1]

Sickle cell disease is associated with hypoxia-induced polymerization of the abnormal HbS molecule, followed by red blood cell injury and the sickling process. Consequently, a microvascular occlusion (vaso-occlusion) can occur and clinically manifest as hemolysis and acute painful episodes.[2,3]

Recently, the mortality of patients with SCD has decreased due to the better understanding of SCD physiopathology, allowing earlier diagnostic and therapeutic interventions, such as newborn screening, antibiotic prophylaxis with penicillin, immunization, the use of hydroxyurea, and multidisciplinary assistance.[4] Consequently, reproductive issues will take a higher priority in SCD, such as delay of pubertal development, delay of first pregnancy, complications in pregnancy and postpartum, and the choice of contraceptive method.[4–8]

Although several studies have demonstrated the influence of the HbSS genotype on some sexual and reproductive issues, there are limited data regarding other SCD genotypes.[5,7,9] The objective of this study was to describe the reproductive variables in different SCD genotypes and the influence of the contraceptive method on acute painful episodes among women with the HbSS genotype.

Methods

From September of 2015 to April of 2016, a cross-sectional study was performed on women with SCD. The subjects were between 14 and 47 years of age and had been treated at a Hematology and Hemotherapy Center in Pernambuco, in the Northeast of Brazil. The data were collected by interviewing158 women who agreed to participate in the research and signed the Informed Consent Form. This study is part of a larger project, which was approved by the Research Ethics Board of the institution.

The sociodemographic, reproductive, and clinical data were collected via interview and examination of medical records, where the SCD genotype was checked. We considered painful crises to have occurred when the woman reported some episode of bone pain.

A database was created using the Microsoft Office Excel 2007 (Microsoft, USA) software. In the statistical analysis, we used the mean (standard deviation) when the numerical variable conformed to a normal distribution, and the median (interquartile range) when it was non-normal distribution. The reproductive variables of the different SCD genotypes were assessed by using the analysis of variance (ANOVA) test to compare means, and the Kruskal-Wallis test to compare the medians.

When the ANOVA results indicated statistical significance, we performed the Tukey test. The association between the contraceptive method and the acute painful episodes was evaluated by the Chi-square test. The statistical analyses were performed with Stata version 12.1 (StataCorp LLC, College Station, USA), and the tests were considered statistically significant when the *p*-value was less than 0.05.

Results

A total of 158 women with SCD were included in this study. Their ages ranged from14 to 47 years, with a mean of 28.3 years. Out of the total population, 64.0% were from the metropolitan region of Recife, 86.6% had mixed or African-American ethnicity, 59.5% had 11 or more years of schooling, 36.7% were retired, and 25.3% had no occupation. A total of 54.4% reported the family income to be less than the minimum wage (MW) (►**Table 1**).

As for the genotypes, 134 women (84.8%) had HbSS, 12 women (7.6%) had HbSC, and 12 (7.6%) were identified with Sβ-thalassemia.

The mean age for SCD diagnosis for all women was 6.5 ± 7.4 years. There was a significant difference in the mean age at diagnosis between HbSC (18.9 ± 9.2 years) and the other two groups ($p < 0.001$). A significant difference in the mean age for menarche was observed between the groups with HbSS (14.8 ± 1.8 years) and HbSC (12.7 ± 1.5 years) ($p < 0.001$). There was no difference among the groups with regard to the mean age of first sexual intercourse ($p = 0.119$) and the first pregnancy ($p = 0.248$). The median number of pregnancies was one for HbSS and two for both HbSC and Sβ-thalassemia ($p = 0.510$). The median number of living children was one for all SCD genotypes ($p = 0.427$) (►**Table 2**).

Of the 130 women (82.3%) who reported being sexually active, 93 used contraceptive methods. The majority used condoms (34.4%), followed by combined hormonal contraceptives (33.3%), and only 6.5% reported taking progestin-only contraceptives. However, 63 of 89 (70.8%) women who got pregnant did not plan the last pregnancy, in spite of having received counseling on reproduction (►**Table 3**).

In this study, we investigated the effect of the contraceptive methods on the frequency of acute painful episodes only in the HbSS group, since this is the most severe form of SCD.

We observed 4 or more acute painful episodes per year in 60.0%of the women using combined hormonal contraceptives, in 50.7% of the women using non-hormonal methods, and in 16.6% of those who used progestin-only contraception. There was no statistical difference between the progestin-only and the combined hormonal contraception ($p = 0.072$), and there was no statistical difference when comparing the progestin-only and the non-hormonal methods ($p = 0.118$). (►**Table 4**)

Table 1 Sociodemographic profile of women with sickle cell disease. Brazil, 2015–2016

Variables	n = 158	%
Age (years) (mean = 28.3)		
≤ 19	23	14.5
20–34	93	58.9
≥ 35	42	26.6
Location		
Recife	50	31.6
Other cities in the RMA	51	32.3
Countryside	57	36.1
Ethnicity		
Mixed	99	62.6
African-American	38	24.0 1.3
White	17	10.8
Indigenous	02	1.3
No information	02	1.3
Schooling		
0 to 3 years	07	4.4
4 to 7 years	18	11.4
8 to 10 years	39	24.7
≥ 11 years	94	59.5
Occupation		
No Job/Housewife	40	25.3
Self-employed/Other	27	17.1
Student	33	20.9
Retired	58	36.7
Family Income		
≤ 1MW	86	54.4
1–2MW	36	22.8
> 2MW	29	18.4
No information	7	4.4

Abbreviations: MW, minimum wage; RMA, Recife metropolitan area.

Discussion

The women in this study were predominantly young, of mixed ethnicity, well educated, and of low income families, as would be expected in this population. The diagnosis of HbSC occurred later than in the other groups. There was a delay in the age of menarche in the HbSS group compared with the HbSC group.

The ethnicity data of this study differ from the Brazilian population data, where most of the women with SCD are black.[10,11] This difference of ethnicity can be explained because the women interviewed in this study self-reported to be of mixed ethnicity.

Most of the women reported more than 11 years of schooling. This reflects the findings of another Brazilian study, which showed an increase of schooling level for women over the years. Advances in therapeutics have improved survival rates of women with SCD and thus, there are increasing numbers of women enjoying a better quality of life.[12]

Table 2 Association between sickle cell disease genotypes and reproductive profile. Brazil, 2015/2016

Variables	All the genotypes ($n = 158$)	HbSS ($n = 134$)	HbSC disease ($n = 12$)	Sβ-thalassemia ($n = 12$)	*p*
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age of diagnosis	6.5 (7.4)	5.5 (6.2)	18.9 (9.2)[a]	5.2 (6.8)	$< 0.001^*$
Age of menarche	14.5 (1.9)	14.8 (1.8)[b]	12.7 (1.5)[b]	13.7 (2.0)	$< 0.001^*$
Age of first intercourse	19.4 (4.2)	19.7 (4.4)	18.3 (2.6)	17.1 (2.2)	0.119^*
Age of first pregnancy	22.0 (4.7)	22.2 (4.7)	22.3 (4.7)	19.1 (3.1)	0.248^*
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	
Number of pregnancies	1 (1–2)	1 (1–2)	2 (1–2)	2 (1–2)	0.510^{**}
Number of living children	1 (1–2)	1 (1–1.5)	1 (1–1.5)	1 (1–2)	0.427^{**}

Abbreviations: HbSS, homozygous hemoglobin S; HbSC, hemoglobin sickle cell; IQR, interquartile range; SD: standard deviation. *ANOVA-to compare the means of the HbSS, HbSC and Sβ-thalassemia. **Kruskal-Wallis- to compare the medians of HbSS, HbSC and Sβ-thalassemia.
[a]The difference was in this group (Tukey test).
[b]The difference occurred only between these two groups (Tukey test).

Table 3 Reproductive variables of women with sickle cell disease. Brazil, 2015–2016

Variables	n	%
Sexual activity ($n = 158$)		
Yes	130	82.3
No	28	17.3
Pregnancy history ($n = 130$)		
Yes	89	68.5
No	41	31.5
Unplanned pregnancy ($n = 89$)		
Yes	63	70.8
No	26	29.2
Contraceptive methods ($n = 93$)		
Condom	32	34.4
Combined hormonal	31	33.3
Surgical methods (vasectomy and tubal ligation)	19	20.4
Progestin-only	6	6.5
Others	5	5.4

The higher educational level in this study was not reflected by these women's income. More than half earned a monthly family income of minimum wage or less. These data agree with other studies that show less access to paid labor activity among the population with SCD, possibly due to the high absenteeism caused by the clinical events of the disease.[2,13]

The mean age for HbSS diagnosis was around 5.5 years. This is high, considering that the National Neonatal Screening Program can diagnose hemoglobinopathy at birth. However, the program was established in 2001, when the majority of the women in this study had already been born.[14] The mean age for HbSC diagnosis (18.9 years), which displays milder clinical conditions, was later than that of the other groups.[5]

The mean age of menarche for HbSS was 14.8 years. This result is supported by other studies that showed a delay of menarche for this condition.[7,15,16] The delay in menarche may be associated with a weight deficit and the delay of skeletal development. It seems reasonable to postulate that the phenomenon of vaso-occlusion may interfere with physiologic mechanisms of growth hormone release in these women.[6,9,16] The socioeconomic factors seem to contribute as well to the delay of the menarche in these women. This hypothesis is supported by a study of Jamaican girls by Alleyne et al,[16] which showed that poorer and less educated women experienced their first menstruation later than those in a better economic and educational situation. When comparing the HbSS and HbSC groups, the difference in age of the menarche was statistically significant in accordance with the Jamaican data.[5] The delay of the menarche may occur due to HbSC resulting in fewer vaso-occlusive events and fewer clinical consequences.[5,17]

In this present study, the mean age of first sexual intercourse and of the first pregnancy showed no difference between the genotypes. A Jamaican study comparing women with HbSS to a control group (women without the disease) did not find any difference, suggesting that HbSS does not influence fertility.[16]

The median number of pregnancies of women with HbSS was lower than the median in the other groups; however, there was no statistical significance, possibly due to the small sample size of the other SCD genotypes. Studies relate HbSS to a smaller number of pregnancies due to factors such as reduction in the frequency of sexual intercourse, fear of becoming pregnant due to the high incidence of fetal loss in pregnancy, and increased risk of morbimortality during pregnancy and during the postpartum period.[4,16]

There was no difference in the number of living children among the SCD genotypes, in contrast to the findings by Serjeant et al.[5] According to their data, the women with HbSS had a lower number of living children when compared with women with HbSC. This divergence may be due to the small sample size of women with HbSC in this present study. In

Table 4 Association between the type of contraceptive method and frequency of acute painful episodes in 108 women with homozygous hemoglobin S (HbSS). Brazil, 2015/2016

Contraceptive method	Frequency of acute painful episodes last year				
	Up to 3 episodes/year		4 or more episodes/year		p^*
	N	%	n	%	
Progestin-only ($n = 6$)	5	83.4	1	16.6	0.093
Combined hormonal ($n = 35$)	10	40.0	15	60.0	0.072
Non-hormonal methods ($n = 73$)	36	49.3	37	50.7	0.118
Total	51	49.0	53	51.0	

*Fisher Test.

Brazil, a study showed that most women with HbSS had only one living child.[15] These women have high morbimortality, with increased risk of prematurity, low birth weight, restricted intrauterine growth, and perinatal mortality.[18]

The majority of women who got pregnant reported that they did not plan to get pregnant, despite having received counseling about pregnancy risks. This supports the idea that the final decision in using a contraceptive method is complex, and difficult to assess in quantitative studies.[19,20] In addition to each woman's individual issues, this decision may be influenced by their complex health condition, since there is no robust evidence regarding the safety of various contraceptive methods in women with SCD.[8]

Among the users of contraceptive methods, most mentioned the use of condoms or combined hormonal methods. The frequency of combined hormonal contraceptive use found in this study is greater than the frequency found by Qureshi et al,[21] probably because combined hormonal contraception is the most widespread method in Brazil, according to a population-based survey conducted in 2006.[22]

In the HbSS group, 83.4% of women who used progestin-only contraception had up to three acute painful episodes in the past year, and 40% of the users of the estrogen-progesterone combination had up to three acute painful episodes, but we did not find any statistically significant difference.

The effects of progesterone on the clinical parameters of SCD are still unclear. A systematic review examined the safety of hormonal contraceptive methods used among women with SCD and found that the progestin-only method has been associated with a decrease in painful episodes.[8] Isaacs suggested, in 1967 that the progestin-only contraception methods might increase the stability of the membranes of the red blood cells subject to the sickling phenomenon.[23]

One of the limitations of this present study was the predominance of women with HbSS, and a small number of women with HbSC or Sβ-thalassemia. This poses difficulties in comparing the SCD genotype groups. Prospective studies with larger samples could reveal differences that may not have been observed in this study. Another limitation may be the low frequency of the use of progestin-only contraception, preventing observation of the differences in the frequency of the acute painful episodes among the different contraceptive methods.

Conclusion

In the evaluation of reproductive aspects, only the age of the menarche showed a delay in HbSS women when compared with HbSC women. The contraceptive method used was not associated with the frequency of the acute painful episodes among the HbSS women.

Conflict of Interests
The authors declare no conflict of interests.

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