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Chemokines in pregnant women with sickle cell disease

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ABSTRACT

Pregnancy in sickle cell disease is a problem due to the adverse outcomes related to the disease. Research into the role of chemokines in sickle cell disease is available, but studies investigating the disease in pregnancy are scarce. Our data show the chemokine profiles of pregnant women with sickle cell disease compared with control groups. There were no differences in MCP-1 level among the groups, but IL-8 and MIG were likely related with disease activity. In addition, levels of IP-10 were higher in pregnant women with sickle cell disease and, interestingly, RANTES levels were higher in normal pregnancy when compared to pregnancy in sickle cell disease. More studies should be encouraged to fully elucidate chemokine activity during pregnancy in sickle cell disease.

1. Introduction

Sickle cell disease (SCD), one of the most common hereditary monogenic diseases in the world, is characterized by chronic hemolysis and clinical alterations due to vaso-occlusive crisis (VOC) and consequently, ischemia in different organs and tissues. In SCD, the hemoglobin S molecule contains a β-globin mutation, secondary to the replacement of glutamic acid by valine at the sixth position of the codon [1].

Pregnant women with SCD are at higher risk for both fetal and maternal adverse outcomes, with a higher mortality rate (approximately 11% maternal mortality and 20% fetal mortality) than unaffected pregnancies [2]. Chronic anemia and VOC episodes are among the most frequent complications related to SCD, affecting about 50% of pregnant women with the disease. Obstetric complications in this population, such as infections, abortions, premature labor, and preeclampsia, may occur. Babies are also prone to intrauterine growth retardation, low birth weight, and small for gestational age [2–5], making it even more challenging to understand the pathophysiology of the disease in pregnant women and their offspring.

Pregnancy is a physiologic condition with a paradoxical characteristic, since there is a maternal tolerance of fetal antigenicity and no immunological rejection by the mother, from the conception up until the delivery [6]. $CD4^+$ T cells are essential for a favorable maternal environment, and after activation, they differentiate into either Type 1 helper (Th1) or Type 2 helper (Th2) effector T lymphocytes, according to the pattern of produced cytokines [7]. The Th2 response is essential for the pregnancy and inhibits inflammatory mediators related to the Th1 response, with a consequently favorable outcome for the pregnant woman and her fetus. It is noteworthy that such categorization into Th1 and Th2 responses simplifies the complex network of interactions of the inflammatory cytokines and chemokines which occur in pregnancy [8].

Several inflammatory mediators are involved in the pathophysiology of SCD, but in pregnant women with SCD are also associated with inflammatory responses being elevated during pregnancy [9–15]. During pregnancy, monocytes are involved in fetal allograph tolerance and in delivery. This recruitment of maternal monocytes and granulocytes from maternal blood is induced by the secretion of chemokines, such as interleukin-8 (IL-8) and macrophage chemoattractant protein 1 (MCP-1) [16]. MCP-1 is a major mediator of monocyte/macrophage infiltration at inflammatory sites under physiologic and pathologic conditions [17]. However, IL-8 is related to the chemotaxis of neutrophils and is also associated with several systemic inflammatory diseases. Several studies in pregnant women with preeclampsia demonstrate increased levels of IL-8, when compared to healthy controls [18–20].

While MCP1 and IL8 are involved in the phagocyte chemotaxis, other chemokines are responsible for the migration of T and NK lymphocytes into the tissue, as well as Monokine induced by gamma interferon (MIG/CXCL9) and Interferon gamma-induced protein 10 (IP-

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10), both being responsible for the activation and recruitment of these cells to sites of inflammation [21]. IP-10 is secreted by T lymphocytes, monocytes, splenocytes, fibroblasts, keratinocytes, thyrocytes, and preadipocytes [22].

Some chemokines are considered proinflammatory and their release may be induced during an immune response at the site of inflammation [23,24]. RANTES/CCL5 is one of the most highly expressed cytokines in platelets upon activation, mediates monocyte arrest on inflamed endothelium, and is secreted by many cell types, such as endothelial cells, macrophages, vascular smooth muscle cells, and platelets. The chemokine also promotes vascular inflammation by recruiting other platelets and inflammatory cells [25,26].

Studies with inflammatory mediators as indicators of SCD severity are scarce [27,24], and have not yet been evaluated in pregnant women with SCD. The alteration in serum levels of inflammatory chemokines may interfere with pathogenesis in SCD, and the identification of these markers may help in early diagnosis, prevention, and treatment of the clinical complications of this disease [28,29]. Therefore, the aim of this study is to report the chemokines serum levels in pregnant women with SCD and to compare them with pregnant women without SCD and non-pregnant women with SCD during childbearing age.

2. Subjects and methods

2.1. Subjects recruitment and study location

A prospective exploratory study was performed in 20 pregnant women with sickle cell disease (PSCD), 24 women with SCD in steady state (SCD), 16 healthy pregnant women without SCD (P), and the control group with 17 healthy women of childbearing age without SCD (HC) from the same population. Patients were enrolled between September 2014 and October 2015, when admitted to the maternity section of the Instituto de Medicina Integral Professor Fernando Figueira (IMIP), Recife, Brazil, a tertiary public hospital.

2.2. Clinical aspects of the population with SCD (pregnant or non-pregnant)

The epidemiological characteristics of women with SCD are described in Table 1. They had similar characteristics regarding age, family income, schooling, and parity, allowing comparison between pregnant and non-pregnant groups.

All of the 20 pregnant women with SCD had regular prenatal visits; none of them used hydroxyurea during pregnancy. Most of the deliveries were by cesarean section (70%). The women referred themselves as black or mixed race (85.7%), 33% lived with a partner, and 56.8% received genetic counseling about SCD and pregnancy (data not shown).

Table 2 describes the unfavorable maternal and perinatal outcomes in pregnant women with SCD. Infection (50%) and pre-eclampsia (35%) were the most frequent unfavorable maternal outcomes, and low birth weight (35%) was the most frequent among the perinatal outcomes. VOC was the main clinical SCD complication (85%) and in this study there were no reports of thrombotic events, retinopathies, bone lesions, or malleolar ulcers during pregnancy. All the women were submitted to blood transfusion during pregnancy.

2.3. Data collection

Data on the socio-demographic and clinical aspects were obtained from each patient through a questionnaire.

The diagnosis of SCD was performed at the Hemoglobinopathies Laboratory at the Center of Hematology in Pernambuco (HEMOPE) using high-performance liquid chromatography (HPLC, Variant II/BIO-RAD).

None of the participants had reported recent infection and women with SCD were taking folic acid alone. The blood samples were collected in the second trimester of pregnancy and at least 30 days after the blood transfusion, while the blood samples of non-pregnant women with SCD were collected during the steady state.

The blood samples of the healthy pregnant women without SCD and the of healthy non-pregnant women groups were from a sample database of women with similar ages and socioeconomic status and these blood samples were stored in the Translational Research Laboratory at IMIP.

2.4. Chemokine assays

Plasma was obtained by centrifugation at 1800 rpm (400 **G)** for 5 min and stored at 80 °C for subsequent quantification of MCP-1, RANTES, MIG, and IP-10 levels (pg/mL). Chemokines were measured through flow cytometry (FACS Verse®, Becton Dickinson, Sunnyvale, CA, USA) using beads from the BD™ Cytometric Bead Array (CBA) Human Chemokine Kit (BD Biosciences, Sunnyvale, CA, USA). Samples were analyzed according to the manufacturer's instructions, using FCAP Array software (BD Biosciences).

The concentration of IL-8 was determined in serum samples by

Table 1
General characteristics of the population.

Characteristics	Groups			
	PSCD (N = 20) Mean (SD) Interval	SCD (N = 24) Mean (SD) Interval	P (N = 16) Mean (SD) Interval	HC (N = 17) Mean (SD) Interval
Age (years)	25.5 (6.79) 17–43	26 (6.87) 17–43	27.8 (5.92) 16–33	29.8 (6.2) 18–40
Family Income (number of minimal monthly wages per dwelling)	2 (0.85) 1–3	2 (0.90) 1–3	2.1 (0.89) 1–4	2.6 (1.36) 1–5
Schooling (years)	11 (3.14) 3–15	9 (4.76) 1–15	11.9 (3.31) 4–18	12.3 (3.24) 4–18
Parity (number of children)	0 (1.78) 0–8	1 (1.38) 0–8	0.8 (1.18) 0–4	0.8 (1.05) 0–3

PSCD, Pregnant with sickle cell disease.
SCD, Sickle cell disease.
P, Healthy pregnant women without sicklecell disease.
HC, Healthy women of child bearing age without sickle cell disease.
SD, Standard Deviation.

Table 2
Adverse outcomes in pregnant women with SCD.

Maternal outcomes	N (%)	Perinatal outcomes	N (%)	Clinical complication outcomes	N (%)
Infection	10(50)	Low birth weight	7 (35)	Vaso-occlusive crisis	17(85)
Pre-eclampsia	7(35)	Prematurity	4 (20)	Urinary tract infection	9 (45)
Oligohydramnios	3(15)	Stillbirth	3 (15)	Respiratory infection	6 (30)
Placental insufficiency	2(10)	Fetal growth restriction	2 (10)	Acute thoracic syndrome	4 (20)
Placental abruption/Placenta previa	2(10)	Perinatal death	1 (5)	Pulmonary arterial hypertension	3 (15)
Eclampsia	1 (5)	Miscarriage	1 (5)	Sepsis	1 (5)

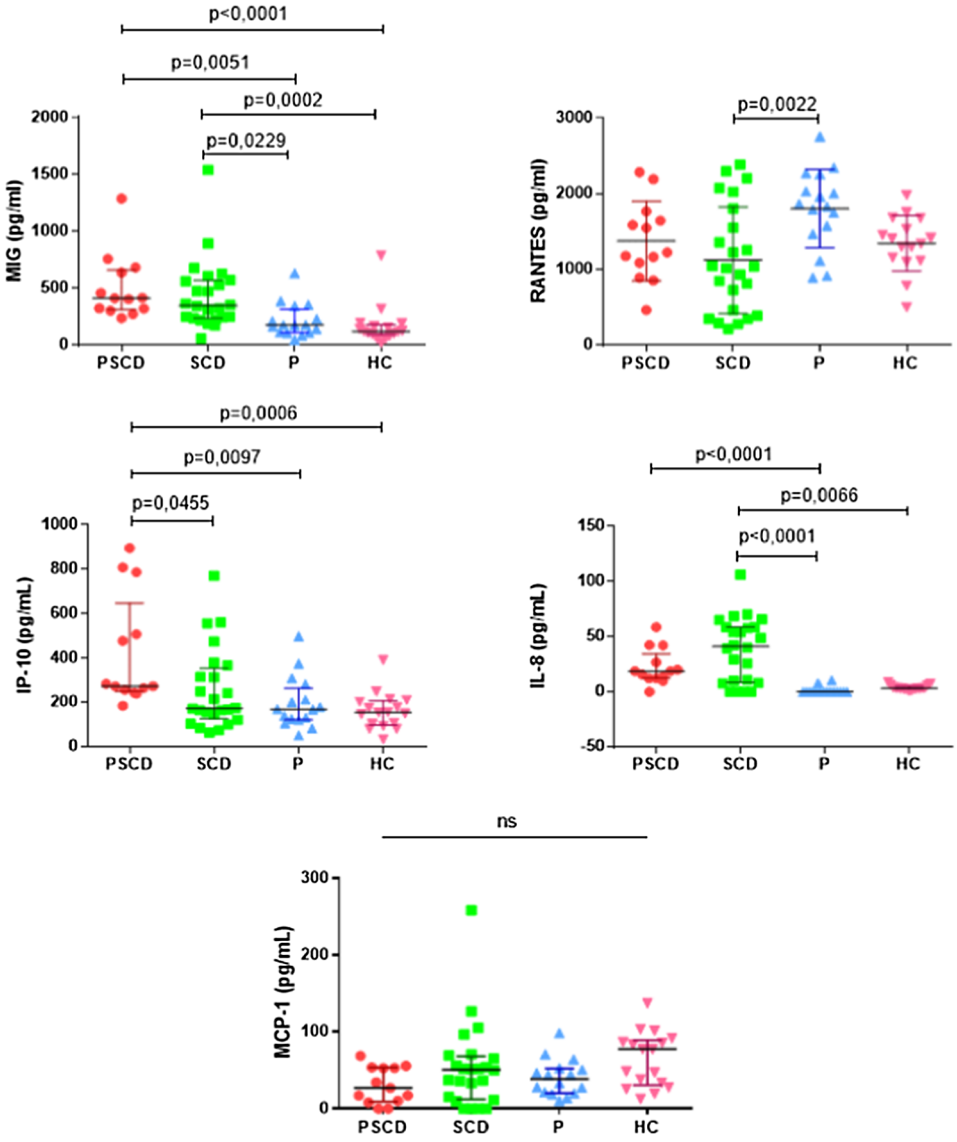

Fig. 1. Analysis of plasma MIG, RANTES, IP-10, IL-8, andMCP1 between PSCD, SCD, P, and HC groups. MIG, Monokine induced by gamma interferon; RANTES, Regulated on activation, normal T-cell expressed and secreted; IP-10, Interferon gamma-induced protein 10; IL-8, Interleukin 8; MCP-1, Macrophage chemoattractant protein 1; PSCD, Pregnancy with sickle cell disease; SCD, Sickle cell disease without pregnancy; P, Healthy pregnant women without sickle cell disease; HC, Healthy controls.

enzyme-linked immunosorbent assay (ELISA) using the BD OptEIA™ Human ELISA Set kits (BD Biosciences, San Diego, CA, USA) according to the manufacturer's instructions. Immediately after performing the assays, the absorbance of the reaction was read by a microplate reader (HUMAN®, Germany) at 450 nm wave length. The concentration of IL-8 was calculated from standard curves using the absorbance values of the standards provided by the manufacturers. Concentrations are expressed in pg/mL.

2.5. Statistical analysis

The analyses were performed among the three gestational trimesters and no statistical difference was observed among them. The second trimester was chosen because it represented the lowest loss of participants during the follow up.

Chemokine levels were not normally distributed according to ÐAgostino-Pearson omnibus normality test. A Kruskal–Wallis test was

used to compare multiple groups.

Correlation between chemokine levels and trimester of pregnancy was assessed using Spearman's non-parametric correlation test. Statistical significance was defined as $p < 0.05$. Data analysis was performed using GraphPad Prism v6.0 (GraphPad Software, San Diego, CA, USA).

The study was approved by IMIP's Research Ethics Committee (4060–14) and written informed consent was obtained from all participants.

3. Results

3.1. Serum levels of chemokines in patients and controls

Fig. 1 summarizes the chemokine levels (MIG, RANTES, IP-10, IL-8, and MCP1) measured in this study

MIG measurements showed statistical significance when comparing pregnancy with SCD (PSCD) with the healthy controls (HC) ($p < 0.0001$) and comparing SCD without pregnancy (SCD) with HC ($p = 0.0002$). The comparison between PSCD and pregnant women without SCD (P) showed that there were higher levels of MIG in the PSCD group ($p = 0.0051$). There was also a significant difference between the SCD group and the P group ($p = 0.0229$). There were no differences between the PSCD and SCD groups (p = ns) or between the P and HC groups (p = ns).

When observing the RANTES measurement results, the only significant difference occurred between SCD and P, with higher levels of RANTES in P ($p = 0.0022$). The levels of IP-10 were higher in the PSCD group when compared with the SCD group ($p = 0.0455$), the P group ($p = 0.0097$), and the HC group ($p = 0.0006$). The measurement of IL-8 showed that the P group presented lower levels of this biomarker when compared with the SCD group ($p < 0.0001$) and with the PSCD group ($p < 0.0001$). The level of IL-8 in the SCD group was higher than in the HC group ($p = 0.0066$). The concentration of the chemokine MCP-1 showed no differences between the groups analyzed in this study.

4. Discussion

Several inflammatory biomarkers are involved in the pathophysiology of SCD, but in pregnant women with SCD, this has not yet been fully elucidated. There was no maternal mortality in our study, despite the high rates of maternal mortality in pregnant women with SCD evidenced by Villers et al. [30]. In a study by Oteng et al., lower maternal mortality frequency was associated with countries with a high gross national income [31]. Ngô et al. also reported a higher maternal mortality rate in pregnant women with SCD, compared with controls, in contrast to our study [32].

Adverse perinatal outcomes in pregnant women with SCD were demonstrated by Oteng et al. [31] and Boga et al. [33], who presented an increased risk of stillbirth in pregnancy with SCD. In this study, low birth weight, prematurity, stillbirth, and fetal growth restriction were the most common adverse perinatal outcomes. Some authors reported a high rate of preterm delivery, cesarean section, infections, pre-terms births, and small for gestational age in SCD when compared to the non-SCD pregnant group [32,34,35].

In view of perinatal outcome in pregnant women with SCD, we performed an analysis of chemokine levels, including as IP-10. IP-10 was higher in pregnant women with SCD compared to other groups and may be responsible for the inflammatory response. IP-10 could be an effective biomarker to evaluate inflammatory status in pregnant women with SCD. Some authors have suggested a relationship between IP and 10 and pregnancy with pre-eclampsia, intra-amniotic inflammation, chronic chorioamnionitis, and spontaneous preterm birth [36–39]. On the other hand, Haedersdal et al. [40] reported that IP-10 could not be used as a prognostic biomarker for pre-eclampsia, intrauterine growth restriction, and spontaneous preterm birth.

Analysis MIG concentration found alteration of these chemokines in non-SCD pregnant women, corroborating with the literature reports [41]. MIG could be a biomarker of the SCD activity but would not be a suitable biomarker to correlate unfavorable outcomes in pregnant women with SCD.

Chemokines are involved in the promotion (IL-8) and inhibition (IP-10 and MIG) of angiogenesis, depending on their structure [42]. MIG and IP-10 have been linked to pulmonary inflammation dysfunction in a murine SCD model [41]. There are also studies that show decreased levels of these chemokines in SCD patients when compared to controls [43]. Besides inflammation, angiogenesis is another important process of new blood vessel growth and is a critical biological step under both physiological and pathological conditions, such as SCD. Angiogenesis can occur under physiological conditions that include embryogenesis and the ovarian/menstrual cycle, but can also be associated with certain pathological conditions such as chronic fibroproliferative disorders [43].

In the analysis of pregnant women with SCD, we demonstrated data that corroborate with the importance of IL-8 in SCD activity. Statistical differences were verified between groups with and without SCD, suggesting IL-8 is asa chemokine related to the SCD and not to pregnancy. IL-8 has been implicated in endothelial cell, monocyte/macrophage activation, and neutrophil recruitment. Changes in the inflammatory biomarker balance in SCD patients is an important risk factor for the occurrence of clinical events, and increased serum levels of circulating IL-8 has been associated with VOC events [44,45]. The MCP-1 results presented in our study are different from those reported in the literature for complications inherent to gestations, as well as in SCD. In pregnant women with SCD, MCP-1 showed no inflammatory role in this study, suggesting that this biomarker may not be a marker of inflammatory reaction in women with SCD. Some studies have suggested that elevation of MCP-1 is a marker of renal disease in SCD [46,47].

The role of MCP-1 during delivery was suggested by its presence in the myometrium and gestational membranes during full-term labor and in amniotic fluid during preterm labor. Circulating levels of MCP-1 are found to be increased in women with gestational complications such gestational diabetes [48]. The detection of MCP-1 at implantation suggests its likely involvement in monocyte and macrophage recruitment for the decidua [49].

In humans, RANTES is produced by T cells, macrophages, endothelial cells, and gestational tissue [50], is an important chemokine for pregnancy maintenance, and is also elevated during early abortion, preterm delivery, and infection [25]. RANTES expression in the placenta, maternal, and fetal serum was detected at a higher level in women with pre-eclampsia compared with normotensive controls [51]. In this study, there was no observed changes in the level of RANTES between pregnant and non-pregnant women with SCD.

We observed low levels of RANTES in non-pregnant women with SCD when compared to healthy pregnant women. This suggests an important role of platelet-derived inflammatory mediators in process of chronic inflammation and thrombotic activity, which are common features of SCD [52]. Platelet activation is associated with endothelial injury present in acute vascular occlusion in SCD [53]. Some patients with SCD that presented gene variations of RANTES had a lower risk of recurrent infections, suggesting a protective effect of this chemokine [54]. The platelets interact with a broad variety of microbial pathogens, likely enhancing pathogen clearance from the bloodstream. Platelets stimulated through interactions with microbes, or their pathways, generate reactive oxygen species that exert direct antimicrobial activity [55–57].

This study is the first of its kind to evaluate chemokines in pregnant women with SCD and could serve as a basis for future researches, to improve the understanding of the mechanisms of chemokines in adverse outcomes in pregnant women with SCD. The same chemokines studied here were found to be relevant in a previous article in pregnant women with and without alloimmunization [58]. We believe that the

chemokines have the potential to be predictive biomarkers of adverse outcomes in pregnant women with different associated pathologies. New studies should be encouraged to improve knowledge of the chronic disease pathogenesis and clinical management.

5. Declarations of interest

None.

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