



Original article

Interleukin-6 in pregnancy with sickle cell disease



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ABSTRACT

Background: Despite advances in health care for sickle cell disease patients, as well as in the improvement in reproductive issues mainly in women with the disease, pregnancy is still a challenge, both for the mother and the child, with high rates of maternal and fetal morbidity and mortality. Besides their chronic hemolytic status and vaso-occlusive events that confer systemic complications, pregnant women also have higher rates of pain episodes, infections, abortion, intrauterine growth retardation, pre-term births, eclampsia, stillbirth and the hemolysis, elevated liver enzymes and low platelets syndrome. The physiologic mechanisms of the disease in pregnancy are still unknown and chronic inflammatory responses may interfere in the adverse outcomes. The cytokine and chemokine profiles in pregnancy with sickle cell disease remain unknown. The aim of this study was to evaluate the cytokine profile of the inflammatory response of pregnant women with sickle cell disease.

Method: Blood samples from 20 pregnant women with sickle cell disease, 24 women with sickle cell disease in steady state, 16 healthy pregnant women and a control group with 9 women at childbearing age were assayed for interleukin-6.

Main results: Pregnant women with sickle cell disease presented high serum levels of interleukin-6, compared to healthy pregnant women ($p = 0.0115$).

Conclusion: These data suggest that the increased production of interleukin-6 may occur during pregnancy with sickle cell disease and that the role of this cytokine in the sickle cell disease pathophysiology and pregnancy complications should be further studied.

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Table 1 – Hematological parameters of the SCD population.

Characteristics	PSCD (n = 20) Median (IQR)	SCD (n = 24) Median (IQR)
Age (years)	25.5 (21–29.5)	26 (21–33.5)
Hb (g/dL)	8.05 (7.1–9.1)	7.7 (7.2–8.6)
MCV (fL)	96.4 (86.7–104.7)	94.1 (82.6–97)
MCHC (fL)	32.8 (32–33.9)	34.1 (33.6–35.2)
MCH (fL)	32 (30–35.6)	31.3 (28.1–33.8)
White cell count ($\times 10^9/L$)	13.7 (10.2–17)	10.9 (9–12.5)
Platelet count ($\times 10^9/L$)	448.5 (412–536.5)	401 (291–517)
Reticulocyte (%)	6.5 (5–10)	11.9 (7.3–27)
LDH (U/L)	392 (294–533)	421 (353–576)
Indirect bilirubin (mg/dL)	1.43 (1.2–1.7)	1.5 (0.6–2.3)

SCD: sickle cell disease; PSCD: pregnant with SCD; IQR: interquartile range (25–75th); Hb: hemoglobin; MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration; MCH: mean cell hemoglobin; LDH: lactate dehydrogenase.

The study was approved by the IMIP Research Ethics Committee (CAAE: 28045814.1.00005201) and written informed consent was obtained from all participants.

Results

The hematological parameters of women with SCD had similar aspects, as shown in Table 1. None of the participants had reports of recent infection. All women with SCD were taking folic acid and all pregnant women with SCD were transfused during pregnancy. The women with sickle cell disease were not under use of hydroxyurea and were in steady state.

In our study, the analysis of IL-6 had higher levels in pregnant women with SCD, compared to pregnant women without SCD ($p = 0.0115$). There were no statistical differences between the other groups of comparison. Graph 1 summarizes the data on IL-6 in the different groups.

Discussion

Sickle cell disease, globally the most common genetic disorder, is a chronic inflammatory condition characterized by elevated levels of inflammatory cytokines, IL-6 being a cytokine associated with pro-inflammatory effects also on tissue homeostasis, regeneration, and metabolism in different diseases.^{13–15}

Pregnancy is also a situation where a perfect regulation of the maternal immune system results in successful outcomes for the mother and fetus. In some pathological conditions such pre-eclampsia, rheumatologic diseases and preterm, immune responses are altered.^{16–19}

The physiological changes of pregnancy will exacerbate the pathophysiological state in SCD. Pregnancy worsens anemia, increases risk of infection, exacerbates the procoagulant tendency of pregnancy and increases the frequency of pain crises. There are some potential mechanisms associated with this, but the exact mechanism is still unknown.^{20–23}

The current clinical management of pregnant women with sickle-cell anemia is still a challenge, as these women could be at risk of becoming critically ill in this period. There is an increased risk of a longer hospitalization stay, an elevated risk of deaths and worse outcomes for the women and for the

concepts, such as preterm, abortions, gynecological bleeding and small size for the gestational age.^{11,24–26}

Despite the importance of the clinical aspects in pregnant women with SCD, immunologic biomarkers may be implicated in the unfavorable outcomes in this group of patients that have not yet been elucidated. The results presented here can be attributed to the inflammatory activity of SCD overlapping the intrinsic inflammation from gestation.^{17,27}

Early identification of biomarkers in pregnant women with SCD who will present gestational complications is critical and may be useful in predicting which of them will present unfavorable outcomes. Currently, there is no evidence of biomarkers in pregnancy in patients with SCD. The IL-6 is a cytokine involved in the regulation of the acute phase inflammatory responses, which, in addition to vaso-occlusive events, are higher in SCD individuals, when compared to healthy ones.²⁸

In the context of pregnancy, IL-6 is required for the immune adaptations in healthy pregnancies and there are reports on elevated levels of IL-6 at the onset of spontaneous abortion, preterm delivery, chorioamnionitis and other obstetric complications.²⁹

Although this study is an exploratory one, presenting a limited number of participants, it was possible to verify a statistical difference in serum levels of IL-6 between pregnant women with SCD and pregnant women without SCD, making it possible to assume that there may exist some relationship between the unfavorable outcomes in pregnant women and SCD, when compared to healthy ones.

The increase in the inflammatory response verified in pregnant women with sickle cell disease could be attributed to the SCD itself, as it is a disease with continuous and chronic inflammatory stimuli in patients afflicted by it. The inflammatory aspects of SCD have already been described in previous studies, but on pregnancy there is still a lack of articles.^{30–35}

Distinguishing the precise role of IL-6 in a SCD pregnancy is a diagnostic challenge in these critically ill patients. This determination is important, with distinct differences in the management and prognosis of each specific clinical entity. Biomarkers have increasingly been utilized in clinical diagnosis and decision making.^{36,37}

Due to the small size of the sample analyzed here, and consequent impossibility to infer causality, the results suggest

that both pregnancy and SCD may play a role in the elevation of this cytokine and this study is one of the first ones to describe this field of investigation.

Conclusion

Both pregnancy and SCD may have played a role in the IL-6 elevation. It is also important to know whether these cytokines are consistently elevated and there is a need to establish a panel of validated biomarkers in pregnant women with SCD. More studies with large samples are necessary to verify the prognostic and predictive value of biomarkers in pregnant women with SCD.

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Conflicts of interest

The authors declare no conflicts of interest.

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