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LEARNER - A prospective, randomized controlled study to evaluate the effects of daily low dose aspirin in pregnant women with sickle cell disease when initiated at the first trimester versus the second trimester of the gestational period – study protocol

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ABSTRACT

Background: Pregnancy in women with Sickle Cell Disease (SCD) is associated with an increased risk in severe complications, such as eclampsia, pre-eclampsia, maternal death, intrauterine growth restrictions, perinatal mortality, and low birth weight. Since 50% of these patients are now living to reproductive age, the management of SCD during pregnancy has become pertinent. Searching for prophylactic and affordable measures for early prevention of these complications is urgently needed.

Methods: Daily low dosage of Aspirin is widely used during pregnancy to prevent pre-eclampsia and other vascular disorders. But the lack of evidence of effectiveness in SCD pregnant women leads to the need to develop clinical trials with this population. In this prospective controlled study, we intend to evaluate the effects of daily low-dose aspirin in pregnant women with SCD, testing the hypothesis that if daily used of low-dose aspirin is initiated early in pregnancy (between 6 and 13 weeks of gestation) versus in the second trimester (between 14 and 27 weeks of gestation), it reduces the incidence of preterm birth mother mortality and miscarriage.

Discussion: The expected impact of the proposed project includes reducing maternal and children mortality due to SCD and reduce the morbidity in pregnancy and delivery.

Trial registration: This study was registered at ClinicalTrials.gov Trial registration: NCT06417411) in May 16th 2024.

1. Background

Sickle Cell Disease (SCD) is a severe hematological hereditary disease and a major concern worldwide since it affects more than 7 million people worldwide. Its incidence is especially higher in sub-Saharan Africa countries, constituting 1000 to 2000 per 100,000 live births [1]. In Angola the prevalence of SCD can reach 3% and the carriers of this recessive mutation are over 20% [2]. Marked by severe complications such as acute vaso-occlusive crises, severe anemia, acute chest syndrome, multi-organ damage and stroke [3], mortality burden associated with this disease is also extremely high in sub-Saharan Africa, where the number of deceased estimated was 2.2% (1.5-3.0) of all deaths in children younger than 5 and 4.3% (3.5-4.6) in individuals from 15 to 49 years of age [1].

Estimates say that 50% of women with SCD are now surviving to childbearing age [1], and become pregnant. As expected, in a severe

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disease as SCD, with all its related complications, pregnancy is associated with an increase in severe outcomes, affecting mother and fetus. Intrauterine growth restrictions, perinatal mortality and low birth weight are associated with SCD pregnancy and there is an increased risk of development of eclampsia, pre-eclampsia and maternal death [4].

Acetylsalicylic acid (ASA), universally known as aspirin, is a widely prescribed medication to prevent cardiovascular complications and in pregnancy, in a daily low dose, to prevent pre-eclampsia and other vascular disorders [5]. With daily low-dose ASA the incidence of pre-eclampsia can be reduced in 28% (RR 0.72, 95% CI 0.62–0.83) in women at high risk for preeclampsia [6]. Although usually prescribed after 12 weeks of gestational age, a randomized, double-blind, placebo-controlled trial (ASPIRIN), performed in more than 11,000 pregnant women, showed that the use of low-dose ASA daily from 6 weeks of gestational age should be considered safe and is effective in lowering the rates of preterm delivery, fetal loss and perinatal mortality, in nulliparous women with a singleton pregnancy [7].

Unfortunately, the number of studies/clinical trials is extremely low, concerning the use of ASA in SCD pregnant women. A small retrospective study in Jamaican women with 120 patients with sickle hemoglobinopathy, 43% taking ASA, showed that women who were not on ASA had more miscarriages and were less likely to have a live birth ($p = 0.005$) [8]. In 2020, a Nigerian trial (PIPSICKLE) started and is comparing a daily dose of 100 mg of ASA (from 12/16 weeks of gestational age till 36 weeks) to a placebo, in pregnant HbSS or HbSC women, with the primary outcome being the incidence of birth weight below 10th centile for gestational age, incidence of miscarriage or perinatal death, but no results were published yet [9].

Although the lack of evidence of effectiveness of the use of ASA in SCD, an international Delphi panel, as agreed that for preeclampsia prevention in SCD patients, ASA should be given prophylactically to pregnant women gestational age between 12 and 36 weeks, although, no consensus was achieved on the respective dosage [10]. Also, the British Society of Hematology (BSH) recommends the use of low dose ASA in SCD pregnant women, at a 75-150 mg daily dose, for those who are at severe risk of pre-eclampsia, and don't present sensitivity to ASA, after 12 weeks of pregnancy [11]. But a recent meta-analysis evaluated the results of 23 clinical trials (not on SCD pregnant women), and reflecting on both effectiveness and side-effects, considered the optimal dosage of ASA to be 80-100 mg (lower than the recommended by the BSH), for preventing pre-eclampsia in high risk pregnant women [12].

In this prospective, randomized controlled study, we intend to quantify the reduction in preterm delivery, perinatal death/miscarriage, and the risk of other maternal and fetal complications, evaluating the effects of daily low-dose ASA (100 mg) in pregnant SCD women if initiated at the first trimester (6-13 weeks) versus the second trimester (14-27 weeks) of the gestational period. The main goal is to demonstrate that first trimester initiation of low dose ASA daily, in pregnant women with SCD, is more effective at preventing maternal and/or fetal complications than starting aspirin at the second trimester. Secondary goals include building capacity in Angola for the conduction of clinical trials involving local research sites and hospitals, through increasing community and patient awareness of clinical research studies, highlighting the ability to collect and analyze data accurately in a timely manner, building clinical trial workflows and electronic data capture guidelines to be use in future clinical trials.

This study was registered at ClinicalTrials.gov Trial registration: NCT06417411) in May 16th 2024.

2. Methods/design

LEARNER is a prospective controlled study to evaluate the effects of daily low dose aspirin in pregnant women with SCD, testing the hypothesis that if initiated early in pregnancy (between 6 and 13 weeks of gestation) reduces the incidence of preterm birth mother mortality and miscarriage, compared to initiation in the second trimester of pregnancy (between 14 and 27 weeks of gestation). The intervention is not blinded, as researchers, clinicians, and participants are aware of the timing of aspirin initiation and the treatment being administered. This 2 years project started recruitment in March 2024 and is being conducted under the oversight of the Instituto de Investigação em saúde de Angola (INIS)/ Centro de investigação em Saúde de Angola (CISA). Data collection, analysis, and management is being conducted by a multidisciplinary team from CISA/INIS, ClinCoord Services (CCS) and Escola Superior de Tecnologia da Saúde de Lisboa (ESTeSL/IPL). All the data collected during the project will be kept strictly confidential and will be stored in a secure central electronic database by the principal investigator.

A **cohort** of 450 pregnant women with SCD will be enrolled in this study. Considering a drop off rate of 20%, sample size was calculated based on previous studies that indicate a 21% incidence of prematurity in SCD pregnancies [4,13] and the expectancy of a 50% reduction by using the daily low dose aspirin, with an 80% power at 5% significant level (number minimum of participants 376, 188 per arm). To reduce the number of lost to follow up patients, the participants' phone numbers as well as phone numbers of their spouse and close relatives are recorded at enrolment, which is clearly described in the informed consent form. If they do not attend their appointments, the research team sends reminder text messages or calls.

Recruitment is taking place in two maternity hospitals in Luanda, Angola (Maternidade Lucrécia Paim and Hospital Materno Infantil Dr Manuel Pedro Azancot de Menezes). In each site, a trained co-investigator who is also an obstetrician/gynecologist, a trained nurse, and a trained laboratory technician will be present.

Inclusion criteria comprise being 15 years old or older, singleton fetus pregnancy, 24 weeks of gestation or less at recruitment (estimated from the last menstrual period or by an early ultrasound scan), attending one of the preceding maternities or any health commodities in the neighboring area, willing to attend regular consultations and consent to participate in the study. Pregnancy in the third trimester (after week 27), HIV infection, diabetes mellitus, chronic hypertension, liver disease (measured by laboratory indication being 3 times above the upper limit of normal), sickle nephropathy, multiple pregnancy, hypersensitivity to aspirin, history of blood transfusion in the last 3 months or not willing to consent to the study, constitute **exclusion criteria**, since in trials involving sickle cell disease, prior blood transfusions can significantly affect hematologic parameters for several weeks and may therefore confound study outcomes.

Patients with confirmed pregnancy and confirmed SCD diagnosis, and who meet the inclusion and no exclusion criteria, after signing the informed consent, are given 100 mg aspirin once daily. This study has **two treatment arms**, (Arm1) 225 women will start medication in the first trimester (6-13 weeks) and (Arm 2) 225 in the second trimester (14-27 weeks) of the gestational period (Fig. 1). Participants are randomly assigned to the first or second trimester group, based on the time of consenting. In both groups, daily use of low dose aspirin is prescribed from the baseline visit until week 36 of gestation or the time of delivery, whichever comes first. Treatment might be suspended earlier in case of medical decision or if consent is withdrawn.

Participants have regular scheduled study visits every 2-weeks at the antenatal clinic up till 26 weeks of their gestational age, then weekly study visits until time of delivery. Six weeks after delivery, participants will be asked to complete a Follow-Up visit. As needed, unscheduled visits are allowed and are also documented.

At visit 0, participants sign the informed consent, then have two weeks to complete all study eligibility criteria. The study team assesses patient eligibility by completing all the screening procedures and by filling out the Inclusion/Exclusion criteria checklist. The screening procedures include completing the patient's SCD and concomitant medical history, patient demographics, forms, vital signs (including weight), pregnancy test, any historical laboratory results, the screening hematology lab, a biochemistry panel (including liver function tests), Malaria rapid test, screening ultrasound, prior and concomitant

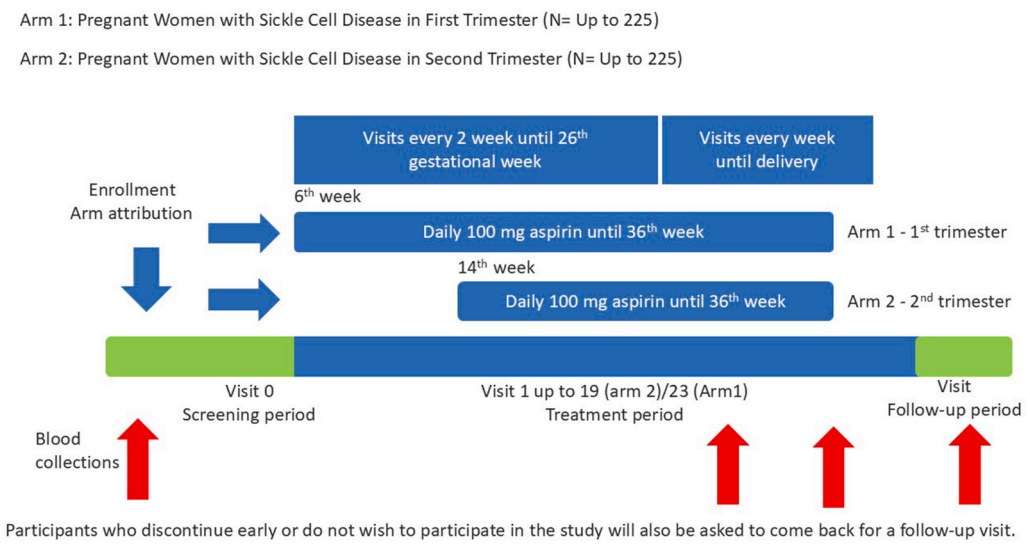

Fig. 1. Trial scheme.

medications log, any adverse events, and an HIV rapid test. Blood samples are also separated for genotyping for the HbS mutation, and other mutations associated with SCD (namely C allele, and possible heterozygotes with Beta Thalassemia). Randomization to a study arm happens at visit 1 (Baseline Visit). All subsequent visits include assessment of vital signs, participant's weight, targeted physician examination, Adverse Event (AE) and Serious Adverse Event (SAE)review, as needed ultrasound, Fetal Doppler Assessment, and prior/concomitant medication review. In addition to the screening visit, blood samples are collections for hematological and biochemical analysis, and urine is collected for urinalysis at weeks 27, 36 and at EoT/ET (End of Treatment/Early Termination).

Aspirin (100 mg) is **distributed** to the patients in blister cards containing the number of pills necessary for 7 or 15 days (depending on the interval between appointments). **Adherence** to the medication is discussed, controlled, and documented at each visit, and empty blisters are to be returned to the site, counted, and kept for monitoring. All appointments, exams or medication will are at no cost for the participants.

The **primary outcomes** of this study are the incidence of preterm births (before 37 weeks' gestational age), maternal mortality up to 6 weeks postpartum and late abortion. **Secondary outcomes** measures include maternal hypertensive disorders, vaginal bleeding, antepartum hemorrhage, postpartum hemorrhage, early preterm delivery (less than 34 weeks, extreme preterm delivery (<28 weeks)) and post-term delivery (≥42 weeks' gestation), small gestational age, perinatal mortality, fetal loss, spontaneous abortion, stillbirth and actual birth weight (<2500 g and <1500 g). Moreover, the project aims to demonstrate a decrease in the manifestation of vaso-occlusive crises and the incidence of pre-eclampsia and infections.

Ethics approval and consent to participate. The study was approved by Angolan Ministry of Health ethical committee, "Parecer n°52/CEMS/2023", and by Agência Reguladora de Medicamentos e Tecnologias de Saúde/Ministério da Saúde de Angola - 99/ARMED/MINSA/2024.

Participants will be asked to sign an informed consent document before they could enter the study.

3. Discussion

LEARNER is expected to produce significant results concerning the efficacy of starting daily low-dose aspirin earlier in pregnancy (1st trimester) in women with Sickle Cell Disease. We suspect that initiating a regimen of low-dose aspirin in pregnant women with SCD, as early as possible, will lead to a reduction in maternal and fetal complications. Therefore, by focusing on the possibility of mitigating these complications, this study seeks to contribute to safer pregnancies for women with SCD, ultimately leading to improved maternal and child health outcomes.

The outcomes are expected to extend beyond the clinical impact. The project holds the potential to significantly reduce maternal and child mortality rates attributed to SCD and its associated complications. Also, the study aims to enhance the involvement of Angolan research institutions in clinical research endeavors. By fostering collaboration between Angolan scientific and medical research establishments and international counterparts, the project aims to create a platform for knowledge and expertise exchange. This collaborative approach aims to contribute to the growth of both local and global research efforts, addressing the unique challenges posed by SCD. In addition, harnessing a data management system efficiently, providing comprehensive team training and having the capacity to enhance the caliber of clinical trials in the region and the future landscape of clinical research in Angola.

Ethics approval and consent to participate

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Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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CRediT authorship contribution statement

Miguel Brito: Conceptualization, Funding acquisition, Investigation, Writing – original draft, Writing – review & editing. **Catarina Ginete:** Conceptualization, Writing – original draft, Writing – review & editing. **Tatiana Gomes:** Conceptualization, Project administration, Writing – review & editing. **Helena Pitangueira:** Conceptualization, Project administration, Writing – review & editing. **Manuela Mendes:** Conceptualization, Funding acquisition, Writing – review & editing. **Ana Furtado:** Project administration, Writing – review & editing. **Ligia Alves:** Conceptualization, Writing – review & editing. **Fernanda Simão:** Project administration, Writing – review & editing. **Mauer Gonçalves:** Conceptualization, Funding acquisition, Writing – review & editing. **Joana Morais:** Conceptualization, Funding acquisition, Writing – review & editing.

Declaration of competing interest

The authors of the manuscript *"LEARNER - A Prospective, Randomized Controlled Study to Evaluate the Effects of Daily Low Dose Aspirin in Pregnant Women with Sickle Cell Disease when Initiated at the First Trimester versus the Second Trimester of the gestational period – study protocol"* declare that they have no financial or non-financial competing interests related to the content of this manuscript.

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Data availability

No data was used for the research described in the article.

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