Title: SAFETY AND EFFICACY OF FERTILITY PRESERVATION IN SICKLE CELL DISEASE AND TRANSFUSION DEPENDENT THALASSEMIA PATIENTS UNDERGOING GENE EDITING THERAPIES

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Background: Sickle cell disease (SCD) and transfusion dependent β-thalassemia (TDT) are autosomal recessive disorders caused by genetic mutations that impair the function of the hemoglobin β subunit. Recent advancements in gene therapy (GT) offer the potential for a functional cure of these conditions. However, the use of busulfan conditioning can result in infertility, making fertility preservation (FP) a critical component of multidisciplinary care. Despite its importance, there is very limited data on the safety and efficacy of FP in individuals with SCD and TDT.

Objective: To evaluate the safety of ovarian stimulation and assess outcomes of oocyte and sperm cryopreservation in individuals with SCD and TDT prior to transplant.

Materials and Methods: This IRB-approved study is a retrospective case series involving patients with SCD and TDT who participated in 4 gene editing clinical trials (NCT03655678, NCT03745287, NCT04853576, and NCT05444894). Participants in the trial were offered fertility preservation services via oocyte or sperm cryopreservation at Nashville Fertility Center. Eligibility included pubertal patients interested in FP without contraindication to oocyte or sperm cryopreservation. Following FP consultation, individualized care plans were developed for each patient.

Results: Table 1 for patient characteristics. On average, female patients underwent 1.3 oocyte stimulation cycles. Male participants underwent an average of 2.4 collections for sperm cryopreservation. The 17 females who underwent oocyte cryopreservation were treated with an antagonist protocol with individualized gonadotropin dosing. Patients were triggered with either leuprolide acetate (n = 17) or choriogonadotropin alfa (n = 5) per physician discretion. A mean of 15 oocytes were cryopreserved in the SCD group (6-37) versus 11.3 in the TDT group (5-24). Males in the SCD group cryopreserved an average of 3.7 vials (1-7) while males in the TDT group cryopreserved an average of 6.4 vials (1-15). All patients with SCD underwent simple or exchange transfusion prior to FP. None of the participants experienced complications during FP, specifically no patients developed sickle cell related vasoocclusive crisis or deep vein thrombosis. Four of the oocyte cryopreservation patients required additional pain medication post-procedure, administered as an outpatient. One patient had her cycle canceled due to poor response.

Conclusion: Recently approved genetic therapies for SCD and TDT necessitate gonadotoxic conditioning, which can lead to long-term complications including infertility. Providing FP options is extremely important for patients pursuing curative options for SCD and TDT. This case series demonstrates that oocyte and sperm cryopreservation is feasible, safe and successful in patients with SCD and TDT. The outcome is similar to what is expected in individuals without SCD and TDT. Special attention should be given to perioperative care and postoperative pain management in patients with SCD.

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Table 1: Patient Characteristics

	SCD	TDT
Average age (yrs)	24.2 (11-34)	18.9 (12-33)
Sex	8 females 6 males	9 females 8 males
Mean AMH (ng/mL)	2.6 (0.6-7.3)	2.8 (1.1-4.26)

Prior Hydroxyurea exposure (%)	100%	12%
Median Hgb prior to procedure (g/dL)	10.1 (8.7-11.4)	11.3 (9.0-12.9)
Median HgS prior to procedure (g/dL)	21.3 (8-45)	N/A