Gene editing for inherited β-haemoglobinopathies: implications of autologous HbF induction in future pregnancies and a framework for antenatal surveillance

Presented at SOHC 2025, Nov 19-21 2025
Hemostasis, transfusion medicine, vascular, laboratory medicine, benign hematology

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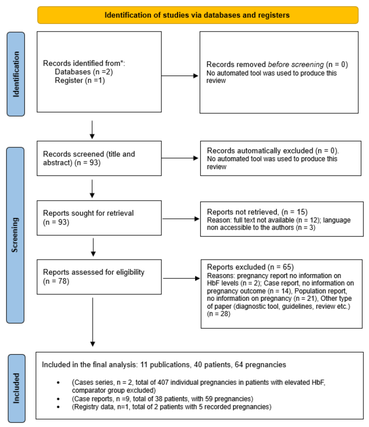
BACKGROUND Somatic gene therapies developed for β-haemoglobinopathies - sickle cell disease and β-thalassemia – aim at stable rexpression of high level of foetal haemoglobin (HbF) are transforming the contemporary therapeutic landscape. HbF, expressed during in utero life and physiologically silenced after birth, has a higher affinity for oxygen allowing for transplacental exchange of oxygen. Its persistence at significant levels in the maternal circulation could impair foetal oxygenation during subsequent pregnancies.

METHODS To anticipate the obstetric risks in this emerging population, we synthesize existing evidence on pregnancy outcomes in women with hereditary persistence of foetal haemoglobin (HPFH)—a naturally occurring model of elevated HbF—to apprehend potential maternal and foetal impacts in individuals having undergone gene therapy for β-haemoglobinopathies.

RESULTS Although the data are too limited to support firm conclusions, these observations suggest that the impact of HbF induction during pregnancy might vary by underlying haemoglobinopathy. In SCD, an HbF level between 10%-50% appears protective while in thalassemia, very high levels (>50%) might be associated with impaired fetal growth (**Figure 1**). Interestingly enough, in those with HbF levels ≥50%—comparable to post-gene therapy levels—rates of fetal growth restriction were markedly higher (**Table 1**). Almost half of neonates (6/13) were <3rd percentile, and an additional 8.3% (2/13) were between the 3rd and 10th centiles. While maternal complications remained modest, mainly anemia (8.3%) and transfusion requirement (13.9%), obstetric outcomes were less favorable, with preeclampsia in 8.3% and low birth weight in 31.5% of cases.

CONCLUSION As gene-editing therapies are offered to teenagers and young adults, and includes fertility preservation prior to myeloablative conditioning, obstetricians and haematologists will be requested to manage post-therapy pregnancies in this population. Evidence strongly suggests that moderate HbF levels (10–30%) reduce both maternal and foetal complications in sickle cell disease. However, levels exceeding 50%, as observed after gene editing in β-thalassemia, might blunt the maternal-foetal oxygen affinity gradient and contribute to placental insufficiency and foetal growth restriction. Multidisciplinary guidelines and dedicated registries will be essential to ensure maternal safety and optimize perinatal outcomes within this evolving therapeutic landscape.

FPRISMA Flow Diagram of Search Strategy
Four different Pubmed database searches were executed with the following keywords: “Pregnancy” AND “hereditary persistence fetal hemoglobin”, “Pregnancy Outcome” AND “Fetal Hemoglobin” and “Pregnancy” AND “delta-beta thalassemia”, “Pregnancy” AND “Hb E-beta thalassemia” on December 10th 2024, yielding a total of 93 references. Abstracts were reviewed for pertinence and a final selection of papers selecting two case series (a third report was excluded, as it presented an interim analysis of the second series) and nine further papers with 59 individual pregnancy descriptions in 38 patients. We added cases from our local registry, identifying two patients with baseline HbF >10% across five pregnancies.



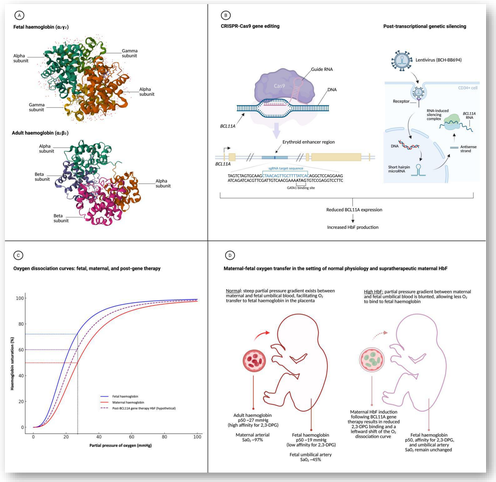
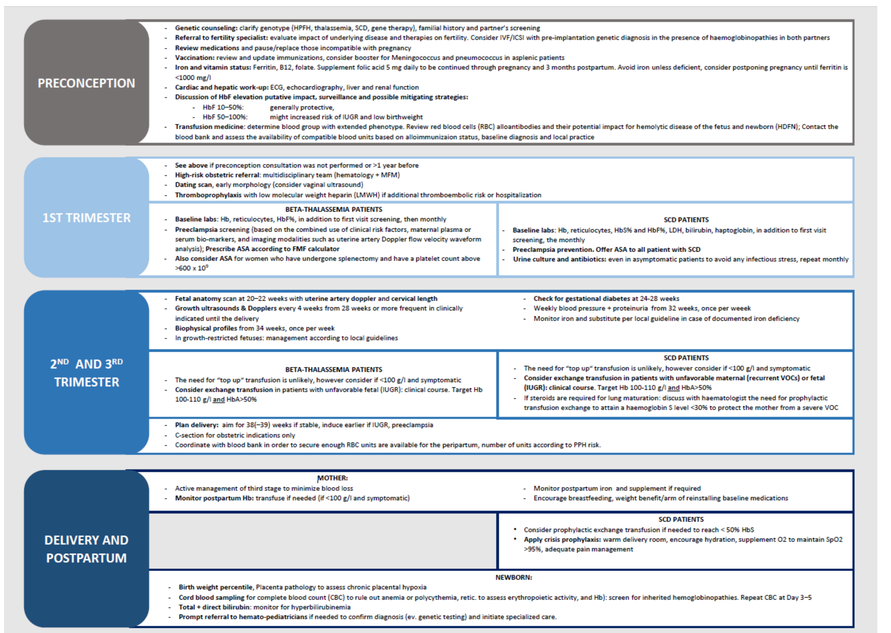


Figure 1 Panel A shows the structural comparison of fetal (HbF) and adult hemoglobin (HbA). HbF comprises two alpha and two gamma subunits, whereas HbA consists of two alpha and two beta subunits. The histidine present in beta chains is replaced by serine in the gamma chain, removing two positively charged residues from the 2,3-DPG binding site; this reduces HbF’s affinity for 2,3-DPG, resulting in a left-shifted oxygen dissociation curve and increased oxygen affinity relative to HbA. **Panel B** shows the CRISPR-Cas9 target site within the erythroid-specific enhancer of BCL11A, directed by a single guide RNA (sgRNA). The GATA1 motif indicates the binding site of the GATA1 transcription factor, essential for enhancer activity in erythroid cells - targeted disruption of this site reduces BCL11A expression, enabling reactivation of HbF. An alternative method of HbF induction involves the transduction of autologous haematopoietic stem cells with a self-inactivating lentiviral vector (BCHBB694) encoding a short hairpin RNA targeting BCL11A, resulting in BCL11A suppression. **Panel C** shows the oxygen dissociation curves for maternal HbA, fetal HbF, and a hypothetical post-gene therapy HbF/HbA mixture profile. At a venous partial pressure of oxygen (~27 mmHg), HbF demonstrates higher oxygen saturation than HbA, facilitating placental oxygen uptake. The hypothetical post-therapy curve is left-shifted, suggesting preserved high oxygen affinity that might impair oxygen delivery in the placenta. Horizontal lines denote saturation levels at 27 mmHg; the vertical line represents the approximate P_{50}. **Panel D** shows the physiological implications of maternal-to-fetal oxygen transfer in normal pregnancy compared with supratherapeutic HbF states.

Table 1. Impact of HbF levels on haematological (maternal), obstetrical and neonatal outcomes. Analysis of the qualitative (thalassemia) subgroup. Abbreviations: β^0 Thal: beta-0-thalassemia, β^+ Thal: beta$^+$-thalassemia, δβ Thal: delta-beta thalassemia, Hb: hemoglobin, HbA: adult hemoglobin, HbE: hemoglobin E, HbF: fetal hemoglobin, HPFH: hereditary persistent fetal hemoglobin, GW: gestational weight, HELLP: hemolysis, elevated liver enzyme, low platelet count, RBC: red blood cell transfusion.

Maternal diagnostic	Hb (g/l)	HbF (%)	Maternal haematological complication	Obstetric complication	GW at delivery	Birth weight (percentile)	Reference	Publication year
HPFH/HbA	NA	10	None	None	38	10-90	[53]	2003
HPFH/HbA	NA	10	None	None	38	10-90	[53]	2003
HPFH/HbA	NA	10	None	None	38	10-90	[53]	2003
HPFH/HbA	NA	10	None	None	39	10-90	[53]	2003
HbE/HbA	119	11	None	None	40	10-90	[47]	2011
HbE/HbA	119	11	None	None	40	10-90	[47]	2011
β0 Thal/HbA	111	11	None	None	40	10-90	[47]	2011
β0 Thal/HbA	111	11	None	None	39	10-90	[47]	2011
β+ Thal/HbA	121	11	None	None	40	10-90	[47]	2011
β0 Thal/HbA	99	13	None	None	41	10-90	[47]	2011
β0 Thal/HbA	104	13	None	None	40	10-90	[47]	2011
δβ-Thal/β0 Thal	111	13	None	None	38	10-90	[47]	2011
δβ-Thal/β0 Thal	125	15	None	None	39	10-90	[47]	2011
HPFH/HbA	NA	15	None	None	NA	10-90	[49]	1986
HPFH/β+ Thal	NA	17,1	Anemia	Anemia	39	<10	[55]	2006
HPFH/β+ Thal	NA	17,1	RBC transfusion	Anemia	39	<10	[55]	2006
HPFH/β+ Thal	NA	17,1	RBC transfusion	Anemia	36	<10	[55]	2006
HPFH/β+ Thal	90	17,4	Anemia	In utero death	36	<10	[55]	2006
δβ-Thal/β0 Thal	104	20	None	None	38	10-90	[47]	2011
δβ-Thal/β0 Thal	130	25	None	Preeclampsia/HELLP	35	<10	[47]	2011
δβ-Thal/β0 Thal	130	25	None	Preeclampsia/HELLP	29	10-90	[47]	2011
δβ-Thal/β0 Thal	130	25	None	Preeclampsia/HELLP	28	<10	[47]	2011
δβ-Thal/β0 Thal	120	26	None	None	38	10-90	[47]	2011
δβ-Thal/β0 Thal	117	28	None	None	39	10-90	[47]	2011
δβ-Thal/β0 Thal	121	29	None	None	40	10-90	[47]	2011
HPFH/HbA	147	35,9	None	None	40	<10	[48]	2019
HPFH/β+ Thal	NA	60	RBC transfusion	None	39	10-90	[55]	2006
β+/β+ Thal	110	70	None	None	38	<10	[47]	2011
δβ-Thal/β+ Thal	91	70	Thrombocytopenia	RBC transfusion	37	<10	[47]	2011
HPFH/β0 Thal	121	80	None	Prematurity	32	10-90	[54]	1994
HPFH/β+ Thal	NA	80,1	None	RBC transfusion	39	10-90	[55]	2006
HPFH/β+ Thal	NA	94,8	RBC transfusion	None	31	10-90	[55]	2006
β0/β0 Thal	86	99	RBC transfusion	None	38	<3	[47]	2011
β0/β0 Thal	86	99	RBC transfusion	RBC transfusion	36	<3	[47]	2011
β0/β0 Thal	86	99	RBC transfusion	RBC transfusion	36	<3	[47]	2011
δβ-Thal/β0 Thal	125	100	Thrombocytopenia	None	39	<3	[47]	2011
δβ-Thal/β0 Thal	125	100	Thrombocytopenia	None	38	<3	[47]	2011
HPFH/β0 Thal	NA	100	None	Prematurity	34	<3	[51]	1992
δβ-Thal/β+ Thal	98	100	Anemia	None	38	10-90	[54]	1994

Table 3 Proposed obstetric guidelines for individuals considering pregnancy after gene-therapy HbF reinduction for SCD or TDT.



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