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RESEARCH ARTICLE

Desire for biological parenthood and patient counseling on the risk of infertility among adolescents and adults with hemoglobinopathies

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Abstract

Background: Both diagnosis and treatment of hemoglobinopathies have been associated with an increased risk of fertility impairment. German guidelines recommend annual monitoring of fertility parameters to enable early detection of fertility impairment and/or to offer fertility preservation (FP) when indicated. We explored

Abbreviations: FP, fertility preservation; FSH, follicle-stimulating hormone; HSCT, hematopoietic stem cell transplantation; HU, hydroxyurea; ISCED, International Standard Classification of Education; RBT, regular blood transfusions; SCD, sickle cell disease; TM, thalassemia major.

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the general desire for parenthood, the frequency of recalling fertility counseling and testing, and the utilization of FP in adolescents and adults with hemoglobinopathies.

Procedure: In a cross-sectional study, patients aged 12–50 years, treated in Germany, Austria, or Switzerland, were surveyed on fertility-related aspects. Medical data, including fertility testing results, were collected from patient records.

Results: Overall, 116/121 eligible patients, diagnosed with sickle cell disease (70.7%), thalassemia (27.6%), or other hemoglobinopathy (1.7%), participated in our study (57.8% female, median age 17.0 years, range 12–50 years). All participants required treatment of the underlying hemoglobinopathy: 68.1% received hydroxyurea, 25.9% required regular blood transfusions, and 6.0% underwent hematopoietic stem cell transplantation (HSCT). Most patients (82/108, 75.9%) stated a considerable to strong desire for (future) parenthood, independent of sex, education, diagnosis, or subjective health status. Fertility counseling was only recalled by 32/111 patients (28.8%) and least frequently by younger patients (12–16 years) or those treated with regular blood transfusions or hydroxyurea. While fertility testing was documented for 59.5% (69/116) in medical records, only 11.6% (13/112) recalled previous assessments. FP was only used by 5.4% (6/111) of patients.

Conclusion: Most patients with hemoglobinopathies wish to have biological children, yet only few recalled fertility counseling and testing. Adequate patient counseling should be offered to all patients at risk for infertility.

KEYWORDS
congenital anemias, fertility impairment, fertility preservation, hemoglobinopathies, parenthood, patient counseling

1 | INTRODUCTION

Life expectancy for patients with hemoglobinopathies, such as sickle cell disease (SCD) and thalassemia major (TM), has significantly improved in recent years,[1,2] with more than 90% of those affected nowadays reaching adulthood in regions with a high developed healthcare system.[1,3] Consequently, enabling the best possible (health-related) quality of life is a central aspect of patient care, which is increasingly being pursued in current treatment strategies.[4,5] Having (biological) children has been reported as a relevant life goal in a small cohort of patients with SCD.[6]

The underlying congenital anemia itself, as well as applied treatments such as regular blood transfusions (RBT) and/or hydroxyurea (HU), have been associated with an increased risk of fertility impairment in both men and women with hemoglobinopathies.[7–14] In addition, conditioning regimens preceding hematopoietic stem cell transplantation (HSCT), which represents a curative therapy option for patients with severe forms of hemoglobinopathies, are gonadotoxic.[7–11] Fertility impairment in patients with congenital anemias include significantly lower sex hormone levels (such as luteinizing hormone [LH], follicle-stimulating hormone [FSH], estradiol), reflecting a hypogonadotropic hypogonadism due to iron overload in the pituitary gland; a prematurely diminished ovarian reserve in women (indicated by low levels of anti-Mullerian hormone [AMH] and high levels of FSH); as well as reduced sperm concentration and motility or abnormal sperm morphology in men.[13–24]

For monitoring fertility in patients with hemoglobinopathies, guidelines from the Germany Society of Pediatric Oncology and Hematology (GPOH), which are also used in Austria and Switzerland, recommend fertility testing in females 13 years and older of age and males 15 years and older.[25–27] Screening should include annual monitoring of hormone levels and additional testing of endocrine function where indicated.[25–27]

Advances in reproductive medicine have made fertility preservation (FP), for example, cryopreservation of oocytes/sperm or ovarian/testicular tissue, a successful option to fulfil the wish for a biological child for patients undergoing treatment potentially impairing fertility.[28–34] If possible, FP should be offered to all patients before undergoing HSCT.[9,28–34] Due to the possible fertility impairment following RBT and HU, FP could also be considered in this patient cohort.[13–24,31]

Patient counseling on aspects of reproductive health in patients with hemoglobinopathies should include the (individual) risk of infertility, the purpose of fertility testing, and information on FP options.

However, an insufficient level of patient education on fertility has been shown among a small number of evaluated patients with SCD.[6,35] With regard to potential fertility issues in patients with hemoglobinopathies, limited data exist on standard practice of fertility counseling and supporting patients in fulfilling their desire for a biological child.[6,36]

1.1 | Objectives

We explored the relevance of fertility-related counseling in a large cohort of adolescents and adults with hemoglobinopathies by (I) assessing their desire for (future) biological parenthood, (II) the frequency of recalling fertility counseling, and (III) fertility testing, as well as (IV) whether they had used FP.

2 | METHODS

2.1 | Study design, setting, and patient recruitment

In this prospective multicenter cross-sectional study, we surveyed adolescent and adult patients with hemoglobinopathies on various fertility-related aspects. Patients were recruited during their regular scheduled appointments through study staff or the patient's treating physician between June 2019 and March 2022 at 10 pediatric or adult hematology departments in Berlin (Germany), Vienna (Austria), as well as Aarau, Basel, Bern, Lucerne, and Zurich (Switzerland). Patients were asked to participate if they met the following eligibility criteria: 12−50 years of age (both inclusive); diagnosed with a hemoglobinopathy; and ability to both cognitively and verbally understand the study and questionnaire in German. The age range applied for inclusion was based on the average age of menarche/spermache (12 years) and the average age of menopause (50 years).[37–39] If patients did not require therapy (either with RBT, HU, or HSCT), they were excluded from the study. Written informed consent to participate in the study had to be given by all patients or, for minors, by their legal guardian. Questionnaire and medical data were documented, processed, and stored pseudonymized, in accordance with data protection regulations. The study was approved by the ethical committee of the Charité–Universitätsmedizin Berlin in Germany (EA2/017/18), Medical University Vienna in Austria (EK Nr:2264/2018), and "Ethikkommission Nordwest- und Zentralschweiz" in Switzerland (EKNZ 2018-02044).

2.2 | Survey methods and data collection

Data were collected using questionnaires, based on surveys from our previous fertility studies in adolescent cancer patients, which were adapted in collaboration with (pediatric) hematologists.[40–44] The survey was designed to investigate several fertility- and reproductive health-related topics, not all evaluated in this publication. It consisted of 14 or 10 items for adolescent female or male patients, respectively, and 25 or 21 items for adult female and male patients, respectively. Questions regarding patients' desire for (future) biological parenthood, previous fertility counseling and fertility testing, as well as utilization of FP did not differ between patients' sex or age, and included (translated from German):

I. How strongly do you wish to be able to have your own children?
II. Were you informed about the potential risk of infertility and possibilities to preserve your fertility?
III. Did you take measures to preserve fertility? (e.g., freezing of sperm/testicular tissue or oocytes/ovarian tissue)
IV. Did you ever undergo fertility testing?

To increase the return rate of completed questionnaires, the survey had to be completed on site. Medical terms, such as "(in)fertility, fertility preservation measures, fertility testing, and so forth," used in the questionnaire were explained before handing out the survey. Adolescent patients were encouraged to ask either study staff or their parents for any question in case of difficulties in understanding or comprehending a survey item. Patient's core data (sex, diagnosis, age, migration background) as well as laboratory/fertility testing results and therapy details, including the quantity of annual blood transfusions and information on HSCT in all patients with hemoglobinopathies, and, specifically for patients with SCD, information on treatment with HU, were collected retrospectively (2012–2022) from digital and analog patient records.

2.3 | Outcomes and influencing factors

Desire for parenthood was assessed using a 4-point Likert scale ranging from no such desire (1) to very strong desire (4). If counseling on potential disease and therapy-related risks of fertility impairment and on utilization of FP could be recalled (yes/no), patients were asked to specify by whom they received the information and whether they had to ask for information themselves. Questions on recalling fertility testing (yes/no) and utilization of FP (yes/no) were followed by specific details on the results of fertility testing and the method of FP, if applicable. Furthermore, patients were asked to report their subjective perception of their current state of health within a 5-point Likert scale ranging from very poor (1) to very good (5), and to give information on sociodemographic data, such as age, country of origin, and their highest level of education.

Patient age was categorized as young adolescents (12−16 years of age), young adults (17−24 years), and adults (≥25 years). Highest level of education was measured according to the International Standard Classification of Education (ISCED 2011), and categorized as *low* (ISCED 1 and 2) or *medium/high* (ISCED 3–8).[45] A patient was considered to have a migration background if the patient or at least one parent did not have German/Austrian/Swiss citizenship at birth. Further, patients were categorized according to their therapy: those who only required RBT, those who (additionally or only) required treatment with HU, and those who underwent HSCT (including patients who had previously received RBT and/or HU).

2.4 | Statistical methods

Data analyses were performed using SPSS (IBM SPSS Statistics for Macintosh, Version 29.0; IBM Corp, Armonk, NY, USA). Univariable analyses, using chi-square or Fisher's exact test with alpha less than 5%, were conducted to assess the desire of biological parenthood, recall of fertility counseling, previous fertility testing, as well as utilization of FP according to sex, age group, level of education, subjective health status, diagnosis, therapy group, or country of the recruiting center using chi-square or Fisher's exact test. All variables used for testing were categorized nominally.

3 | RESULTS

3.1 | Patient characteristics

In total, 116 out of 121 patients agreed to participate in our study (response rate: 95.9%). About half of the participants were female (67/116, 57.8%) and overall median age at time of study inclusion was 17 years (range 12–50 years, Table 1). Of those patients providing information on origin, all (99/99, 100%) stated a migration background, with the largest groups reporting Western African origin (37/99, 37.4%), followed by Middle African (17/99, 17.2%) and Western Asian (15/99, 15.2%) origin. Most patients were diagnosed with SCD (82/116, 70.7%), 32 (27.6%) with TM or transfusion-dependent thalassemia intermedia and two (1.7%) with Hb Mizuho, a rare hemoglobin variant (Table 1). Overall, six patients stated to already have biological children.

3.2 | Desire for (future) biological parenthood

Among patients who reported to not have children (108/114, 94.7%), the majority (82/108, 75.9%) reported a considerable to strong desire to become a parent in the future (Table 2). Throughout all age groups, the desire for biological children was high, with 77.8% in the youngest age group (12–16 years). Young adults (17–24 years) had a stronger wish for children compared to patients 25 years and older (81.0% vs. 50.0%; $p = .057$). Desire for (future) parenthood was high independent of diagnosis and no relevant influence of sex, level of education, or subjective health status on the intensity of desire for biological children was observed (Table 2).

3.3 | Counseling on the potential risk of fertility impairment

In total, 28.8% (32/111) of all patients recalled counseling on the potential risk of fertility impairment, due to their respective disease and/or its treatment, and on FP options. Of these, 90.6% (29/32) stated that fertility counseling was provided by their treating physician, one patient had received counseling from a nurse and two from another, not further specified, person. Six patients (6/32, 18.8%) had to ask for fertility counseling themselves. Univariable analysis showed that younger patients (12–16 years) were informed less frequently than older patients (17–24 years; 16.4% vs. 42.5%, $p = .005$). Almost all patients treated with HSCT (5/7, 71.4%) recalled counseling on the potential risk of fertility impairment and on FP options, compared to patients treated with HU (28.4%, 21/74, $p = .032$) or RBT (20.0%, 6/30, $p = .016$). Patients who considered their subjective health status low recalled counseling to a higher rate than those who felt good or very good (46.9% vs. 18.5% vs. 28.0%, $p = .005$, Table 2). No relevant differences in fertility counseling were seen regarding patients' sex, diagnosis, or level of education. The overall high desire for biological parenthood in contrast to low rates of fertility counseling is displayed in Figure 1.

3.4 | Fertility testing

Overall, 11.6% (13/112) of participants recalled fertility testing in the past. However, medical records from up to the previous 10 years showed that 59.5% of all participants (69/116) had had at least one examination of fertility (sex-specific hormone testing, GnRH stimulation test, and/or spermiogram). Patients who recalled fertility counseling stated having undergone fertility testing more often than patients who did not remember counseling (25.8% vs. 6.5%, $p = .009$). Regarding the country of recruiting clinic, patients treated in Austria could recall fertility testing more often than those treated in Germany or Switzerland (38.5% vs. 2.3% vs. 4.8%, $p < .001$). While the level of education correlated with the frequency of recalling fertility testing (22.0% [medium/high] vs. 4.8% [low], $p = .012$), no differences in regards of sex or age were observed (Table 2).

3.5 | Utilization of fertility preservation

In total, six participants (6/111, 5.4%), aged between 13 and 33 years (mean age 21 years), stated that they had previously used FP measures, including cryopreservation of sperm cells ($n = 2$), cryopreservation of testicular ($n = 2$)/ovarian tissue ($n = 1$), and another, not further specified, method ($n = 1$). Patients recalling fertility counseling had used FP procedures more often than those who could not recall counseling (16.1% vs. 1.3%, $p = .007$). FP utilization was higher in patients who had received HSCT (4/7, 57.1%) than in patients treated with HU (2/75, 2.7%, $p < .001$). Male patients were more likely to having used FP than female patients (10.6% vs. 1.6%). Furthermore, the frequency of having used FP increased with age (12–16 years: 1.8%, 17–24 years: 7.7%, ≥25 years: 11.8%, Table 2).

4 | DISCUSSION

Our findings indicate that reproductive health is an important aspect in the long-term care for patients with hemoglobinopathies. Among this

TABLE 1 Patient characteristics (in total and by gender).

Patients	Total *n* (%)	Female *n* (%)	Male *n* (%)
	116 (100)	67 (57.8)	49 (42.2)
Age at time of survey			
Median age [range], years	17.0 [12–50]	17.0 [12–50]	16.0 [12–33]
12–16 years	56 (48.3)	28 (41.8)	28 (57.1)
17–24 years	42 (36.2)	24 (35.8)	18 (36.7)
25–50 years	18 (15.5)	15 (22.4)	3 (6.1)
Migration background[a]	99 (100)	58 (100)	41 (100)
Western Africa	37 (37.4)	20 (34.5)	17 (41.5)
Middle Africa	17 (17.2)	12 (20.7)	5 (12.2)
Northern Africa	6 (6.1)	1 (1.7)	5 (12.2)
Eastern Africa	3 (3.0)	3 (5.2)	
Western Asia	15 (15.2)	6 (10.3)	9 (22.0)
South-eastern Asia	5 (5.1)	4 (6.9)	1 (2.4)
Southern Asia	7 (7.1)	6 (10.3)	1 (2.4)
Southern Europe	6 (6.1)	5 (8.6)	1 (2.4)
South America	2 (2.0)		2 (4.9)
Caribbean	1 (1.0)	1 (1.7)	
Diagnosis			
SCD	82 (70.7)	48 (71.6)	34 (69.4)
HbSS	74 (90.2)	43 (89.6)	31 (91.2)
HbS beta thalassemia	8 (9.8)	5 (10.4)	3 (8.8)
TM/TI	32 (27.6)	17 (25.4)	15 (30.6)
Hb Mizuho	2 (1.7)	2 (3.0)	–
Level of education			
Low (ISCED 1–2)	64 (61.0)	33 (55.9)	31 (67.4)
Medium/high (ISCED 3–8)	41 (39.0)	26 (44.1)	15 (32.6)
Subjective health status			
Very poor/poor/medium	33 (28.4)	20 (29.9)	13 (26.5)
Good	57 (49.1)	35 (52.2)	22 (44.9)
Very good	26 (22.4)	12 (17.9)	14 (28.6)
Therapy details			
RBT	30 (25.9)	16 (23.9)	14 (28.6)
HU	79 (68.1)	50 (74.6)	29 (59.2)
HSCT	7 (6.0)	1 (1.5)	6 (12.2)
Country of recruiting clinic			
Germany	47 (40.5)	23 (34.3)	24 (49.0)
Austria	26 (22.4)	14 (20.9)	12 (24.5)
Switzerland	43 (37.1)	30 (44.8)	13 (26.5)

Note: ISCED, International Standard Classification of Education: ISCED 1, primary education; ISCED 2, lower secondary education; ISCED 3, upper secondary education; ISCED 4, post-secondary non-tertiary education; ISCED 5, short-cycle tertiary education; ISCED 6, bachelor or equivalent; ISCED 7, master or equivalent; ISCED 8, doctoral or equivalent.

Abbreviations: Hb Mizuho, hemoglobin variant Mizuho; HSCT, hematopoietic stem cell transplantation; HU, hydroxyurea; RBT, regular blood transfusions; SCD, sickle cell disease; TI, thalassemia intermedia; TM, thalassemia major.

[a]Migration background was defined if patient himself/herself or at least one parent did not acquire German/Austrian/Swiss citizenship at birth.

TABLE 2 Desire for biological children, fertility counseling, fertility testing, and utilization of fertility preservation by patient's characteristics.

	Considerable/strong desire for (future) biological children[a]		Fertility counseling		Fertility testing		Utilization of fertility preservation	
	n (%)	*p*-Value[b]	*n* (%)	*p*-Value[b]	*n* (%)	*p*-Value[b]	*n* (%)	*p*-Value[b]
Gender	*n* = 108		*n* = 111		*n* = 112		*n* = 111	
Male	35/48 (72.9)	.513	16/49 (32.7)	.429	6/46 (13.0)	.692	5/47 (10.6)	.081
Female	47/60 (78.3)		16/62 (25.8)		7/66 (10.6)		1/64 (1.6)	
Age at time of survey	*n* = 108		*n* = 111		*n* = 112		*n* = 111	
12–16 years	42/54 (77.8)	.704	9/55 (16.4)	.005	4/54 (7.4)	.195	1/55 (1.8)	.304
17–24 years	34/42 (81.0)		17/40 (42.5)		7/40 (17.5)		3/39 (7.7)	
25–50 years	6/12 (50.0)	.057	6/16 (37.5)	.731	2/18 (11.1)	.706	2/17 (11.8)	.634
Diagnosis	*n* = 108		*n* = 111		*n* = 112		*n* = 111	
SCD	58/77 (75.3)	–	25/77 (32.5)	–	8/79 (10.1)	–	5/79 (6.3)	–
TM/TI	23/30 (76.7)	–	7/32 (21.9)	–	5/31 (16.1)	–	1/30 (3.3)	–
Hb Mizuho	1/1 (100)	–	–	–	–	–	–	–
Therapy			*n* = 111		*n* = 112		*n* = 111	
RBT	–	–	6/30 (20.0)	.016	7/30 (23.3)	.198	–	–
HU	–	–	21/74 (28.4)	.032	6/75 (8.0)	.575	2/75 (2.7)	<.001
HSCT	–	–	5/7 (71.4)				4/7 (57.1)	
Subjective health status	*n* = 108		*n* = 111		*n* = 112		*n* = 111	
Very poor/poor/medium	21/30 (70.0)	.459	15/32 (46.9)	.005	5/32 (15.6)	.490	2/32 (6.3)	.553
Good	41/53 (77.4)		10/54 (18.5)		5/54 (9.3)		1/54 (1.9)	
Very good	20/25 (80.0)	.792	7/25 (28.0)	.340	3/26 (11.5)	.710	3/25 (12.0)	.091
Level of education	*n* = 98		*n* = 100		*n* = 103		*n* = 101	
Low	46/62 (74.2)	.296	16/60 (26.7)	.373	3/62 (4.8)	.012	3/60 (5.0)	.684
Medium/high	30/36 (83.3)		14/40 (35.0)		9/41 (22.0)		3/41 (7.3)	
Desire for (future) children[a]			*n* = 104		*n* = 105		*n* = 104	
No or little	–	–	5/23 (21.7)	–	1/24 (4.2)	–	1/24 (4.2)	–
Considerable or strong	–	–	26/81(32.1)	–	12/81 (14.8)	–	5/80 (6.3)	–
Fertility counseling					*n* = 108		*n* = 109	
Yes	–	–	–	–	8/31 (25.8)	.009	5/31 (16.1)	.007
No	–	–	–	–	5/77 (6.5)		1/78 (1.3)	
Country of recruiting clinic	–	–	*n* = 111		*n* = 112		*n* = 111	
Germany	–	–	8/44 (18.2)		1/44 (2.3)		2/45 (4.4)	
Austria	–	–	11/26 (42.3)	.028	10/26 (38.5)	<.001	–	–
Switzerland	–	–	13/41 (31.7)	.149	2/42 (4.8)	.612	4/41 (9.8)	.418

Abbreviations: FP, fertility preservation; Hb Mizuho, hemoglobin variant Mizuho; HSCT, hematopoietic stem cell transplantation; HU, hydroxyurea; RBT, regular blood transfusions; SCD, sickle cell disease; TI, thalassemia intermedia; TM, thalassemia major.

[a]All results regarding desire for future children were done in patients stating not yet having children only.

[b]*p*-Values in categories of three were each calculated compared to the attribute without a *p*-value in the table.

study cohort, the overall desire for (future) children was high. However, the frequency of recalling counseling on potential risks of fertility impairment remained low.

Most adolescents and young adults with hemoglobinopathies had a considerable to strong desire for (future) biological parenthood. Our findings are similar to those of Nahata et al. who reported that adolescents with SCD receiving HU consider having future children as an important life goal, with two thirds reporting a desire to have a family in the future (*n* = 12/18).[6] We were able to confirm these findings in a much larger, multicenter cohort of patients with hemoglobinopathies requiring treatment. Most importantly, the overall wish for (future) parenthood among our cohort remained high independent of age, sex,

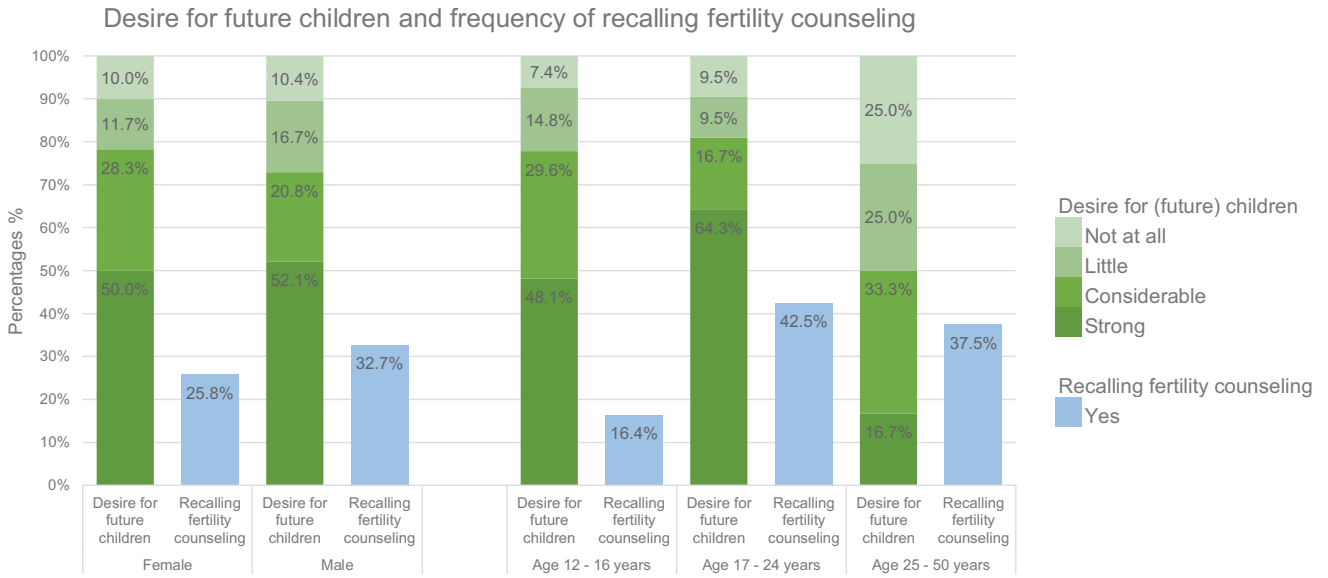

FIGURE 1 Desire for (future) children and frequency of fertility counseling. Intensity of desire for (future) children ranging from "not at all" to "strong" is shown for female and male patients, and for the age groups (12–16, 17–24, and ≥25 years). Percentage of recalling fertility counseling among the respective group is displayed next to the desire of (future) children.

diagnosis, intensity of treatment, level of education, or the subjective health status. Yet, in line with previous research among patients with SCD,[6] the majority of our patients, except patients that had received HSCT, could not recall having received counseling on potential risks of infertility and FP options. Our study findings are especially relevant for countries in which there is no national health program for the management of hemoglobinopathies and might help to raise physicians' awareness on the importance of fertility counseling among this patient cohort.[46–48]

Research shows that several factors, such as patient's age and cultural background as well as physicians awareness and comfort in discussing fertility issues, influence the realization of fertility counseling.[49] In our study, young adolescents were less likely to recall fertility counseling than older patients, whereas no difference was seen regarding sex. Age-related differences in fertility counseling have similarly been reported among cancer patients,[40] and age has been described as an obstacle in physicians to discuss FP, for example, due to lacking prepubertal FP options.[49] It is possible, that the high rate of patients with a migration background influenced the overall low numbers of recalled fertility counseling in this study. Cultural background or potential language barriers could have served as an obstacle to physicians discussing reproductive health with their patients. Patient counseling on fertility can be more effective when supported by additional written information material or digital tools, strengthening both patient's knowledge and empowerment to make educated decisions.[50] Patients with SCD who received an informative brochure on reproductive options reported an empowerment toward future family planning.[51]

The frequency of fertility counseling did not differ regarding the underlying diagnosis; however, the type of therapy regimen influenced the likelihood of receiving counseling. Patients who had received HSCT recalled fertility counseling almost three times more often than patients treated with RBT or HU. These results do not come as a surprise as fertility counseling is recommended for all patients receiving HSCT, due to the known gonadotoxic conditioning regimen preceding transplantation.[52] However, all patients with hemoglobinopathies are potentially at risk for fertility impairment.[7–24] Recommendations for optimized fertility counseling in patients with SCD have been described in a recent article by Meacham et al.,[53] but specific guidelines for fertility counseling are still missing.

Medical records showed that fertility parameters were examined at least once in 59.5% of all patients, pointing out room for improvement in including fertility testing as recommended by the GPOH into routine medical care. Surprisingly, only a minority of our patients could recall previous fertility testing. As, for example, hormone parameters can be evaluated within routine blood check-ups, we argue that physicians may have been aware of potential risks to fertility and monitored hormone parameters. These examinations can be conducted without explicit discussion with the patient, which could explain the discrepancy between medical records and patient recollection of fertility testing.

The overall use of FP was very low in our study. With 48.3% of patients being under the age of 17, one should keep in mind that cryopreservation is not yet commonly used in children. However, examples for FP measures in pre- and pubertal teens have been described.[29,31,33] In general FP should be offered before initiation of a treatment potentially impairing fertility if feasible.[9] In patients with hemoglobinopathies, this is not always possible as treatment, for example with HU, is often started within a very young age. Within our study cohort, FP was mostly conducted in patients receiving HSCT. These findings are in line with the lack of specific recommendations for FP prior to HU treatment or during RBT. While HSCT has been

associated with a drastically reduced fertile window,[9] it remains unclear whether potential side effects of HU on fertility are reversible after ceasing treatment.[16,24,54] Furthermore, the reproductive window in patients receiving RBT has not yet been fully described. Future studies are needed to ensure a better understanding of (in)fertility in patients with hemoglobinopathies receiving HU or RBT. Even in the absence of consistent data and guidelines on fertility for these patients, our study emphasizes the importance of adequate counseling on fertility and FP, as receiving fertility counseling was associated with a higher use of FP.

A further potential barrier to FP in our cohort could have also been the costs for cryopreservation, which had to be covered by families themselves. Prices for cryopreservation and costs for annual storage are set by the respective clinic. For patients undergoing gonadotoxic treatment, such as prior to HSCT, FP has been included in public insurance coverage in Germany since February 2021 and in Switzerland since July 2019. This milestone in patient care enables a more equal access for patients who wish to undergo FP in future.

When interpreting our study findings, limitations of our study setting need to be considered. To minimize bias in sample selection, we asked patients to participate consecutively at their regularly scheduled appointment in the respective clinical department. As data on fertility counseling, previous fertility testing, and FP are based on patients' answers in the questionnaire, we cannot rule out a potential recall bias. The recollection of fertility testing could have possibly been facilitated by changing the question from a yes/no choice to a list of menu items of possible fertility examinations (e.g., spermiogram, hormone parameter evaluation). Furthermore, it would be interesting for future studies to objectively evaluate fertility counseling among participating clinics. This would show if patients' knowledge gap on fertility risks was due to an insufficient, arguably not age- or language-appropriate, communication strategy or if fertility counseling was not provided by the clinical team at all. Even when taking recall bias into account, the lack of recalling fertility counseling could also show that information on fertility-related aspects had not been provided frequently enough for patients to assimilate this information. On the other hand, patients were not asked whether they had informed themselves on certain risks of fertility impairment using other sources, such as websites or patients' organizations, or if patients, who stated lack of counseling, felt sufficiently informed, nonetheless. Although inclusion criteria required patients to have a profound knowledge of the German language, it may be possible that language barriers, especially in terms of medical context, may have contributed to incorrect survey responses. Future studies should take into account to phrase survey items in lay language.

Fulfilling the desire of biological parenthood is an important life goal in patients with hemoglobinopathies throughout all age groups. However, patient counseling on potential risks of fertility impairment and FP is still insufficient. Physicians training in fertility counseling in this young patient cohort (with migration background), as well as guidelines for standardized fertility testing, need to be improved and implemented. For clinical use age- and language-appropriate information material should be developed in collaboration with treating physicians, fertility specialists, psychologists, and affected patients. To support patients toward a self-determined family planning, all patients with hemoglobinopathies should be offered fertility counseling in standard practice.

AUTHOR CONTRIBUTIONS

Study concept by Greta Sommerhäuser, Anja Borgmann-Staudt, Ralph Schilling, and Magdalena Balcerek. Study design and material by Greta Sommerhäuser, Ralph Schilling, and Magdalena Balcerek. Patients were recruited by Anne-Catherine Radauer-Plank, Tamara Diesch-Furlanetto, Monika Schneider, Greta Sommerhäuser, Jill Dülberg, Miriam Diepold, Alicia Rovó, Linet Muthoni Njue, Beatrice Drexler, Laura Infanti, Sabine Kroiss, Ramona Merki, Katrin Scheinemann, Bernhard Eisenreich, Inga Hegemann, and Leo Kager. Data were collected from medical records by Tamara Diesch-Furlanetto, Lucía Alácan Friedrich, Vivienne Salow, Jill Dülberg, Linet Muthoni Njue, Laura Infanti, Sabine Kroiss, Ramona Merki, Katrin Scheinemann, and Ljubica Mandic. Questionnaire data entry by Greta Sommerhäuser, Anne-Catherine Radauer-Plank, and Jill Dülberg. Data harmonization was conducted by Anne-Catherine Radauer-Plank and Magdalena Balcerek. Formal analyses were primarily conducted by Anne-Catherine Radauer-Plank, supported by Ralph Schilling, Stephanie Roll, and Magdalena Balcerek. The manuscript was written by Anne-Catherine Radauer-Plank and Magdalena Balcerek. All authors revised and commented on the paper and approved of the submitted and final version.

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CONFLICT OF INTEREST STATEMENT

Leo Kager has received fees from Novartis, Amgen, Agios, and Bayer, not related to this study. The remaining authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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