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ORIGINAL ARTICLE

Reproductive decision-making by women with X-linked hypohidrotic ectodermal dysplasia

B. Leo,[1,2] H. Schneider,[1,2] J. Hammersen[1,2,*]

[1]Department of Pediatrics, University Hospital Erlangen, Erlangen, Germany
[2]Friedrich-Alexander-Universität (FAU) Erlangen-Nürnberg, Erlangen, Germany
*Correspondence: J. Hammersen. E-mail: johanna.hammersen@uk-erlangen.de

Abstract

Background In X-linked hypohidrotic ectodermal dysplasia (XLHED), ectodysplasin A1 (EDA1) deficiency results in malformation of hair, teeth and sweat glands. Lack of sweating which can cause life-threatening hyperthermia is amenable to intrauterine therapy with recombinant EDA1.

Objectives This study aimed at evaluating reproductive decision-making by women with XLHED and at clarifying the potential impact of a prenatal treatment option.

Methods In a retrospective cross-sectional analysis, a 75-item questionnaire filled in by 50 women with XLHED (age 19–49 years) was assessed.

Results Sixteen women (32%) prevented pregnancies because of the risk to pass on XLHED; 15 considered assisted reproduction for the same reason. Twelve women had a history of miscarriage, stillbirth or abortion, and three women reported on previous abortion of affected fetuses. When imagining to be pregnant, all except one showed interest in prenatal diagnosis of XLHED and in the possibility of treatment before birth. In 13 out of 50 women (26%), XLHED if detected prenatally would have impact on the continuation of pregnancy. Among 35 mothers of at least one affected child, XLHED had rarely been diagnosed during the first pregnancy (17%) but regularly during subsequent pregnancies (77%). Becoming aware of the condition before birth had caused a moral conflict for 50% of these women. Subjects with an affected child less frequently considered assisted reproduction to prevent XLHED ($P < 0.05$). In 69% of the women who reported an effect of XLHED on family planning, a prenatal treatment option for this disease would influence their decision-making.

Conclusions Many pregnant XLHED carriers who seek prenatal diagnosis experience moral conflicts. A prenatal treatment option would have strong impact on reproductive decisions, underlining the importance of adequate professional counselling.

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Conflicts of interest

The authors have no conflicts of interest to report.

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Introduction

Ectodermal dysplasia (ED) refers to a group of inherited defects of ectodermal structures, including skin, hair, teeth, nails and various eccrine glands. The most common form, X-linked hypohidrotic ED (XLHED), is caused by pathogenic variants of the X-chromosomal gene *EDA* that lead to the absence or dysfunction of the signalling protein EDA1 and thus to a characteristic triad of hypotrichosis, missing teeth and hypo- or anhidrosis.[1–5] Additional clinical problems may be dry, eczematous skin, dry eyes, recurrent respiratory infections, missing or peg-shaped teeth, failure to thrive and developmental retardation.[6–8] While generally not affected as severely as hemizygous males, affected females may also suffer from developmental defects of the mammary glands and/or breastfeeding difficulties.[8–10] Physical stigmata and other XLHED symptoms—notably anhidrosis—may cause relevant psychosocial problems in individuals with XLHED.[11–14] Inability to sweat poses male patients at risk of life-threatening hyperthermia, especially in early infancy, and accounts for the high mortality of the disease (2–30%).[15–19]

In a woman with known carrier status of XLHED, prenatal diagnosis of XLHED can be established by molecular genetic testing after amniocentesis or chorionic villus sampling, but also

non-invasively by tooth germ sonography.[20] Treatment of XLHED has been symptomatic so far. Recently, prenatal intra-amniotic injection of a recombinant EDA1 replacement protein in three affected boys was shown to induce the development of functional sweat glands and more teeth,[21] and this novel therapeutic approach is about to be evaluated in a pivotal clinical trial. An option to treat XLHED already before birth could impact reproductive choices made by individuals affected by this genetic disease. In addition, it is largely unknown to what extent female XLHED carriers feel confined in conceiving children. The aim of this study was to evaluate family planning and reproductive decision-making by women with XLHED and to determine the influence of a potential prenatal treatment option on reproductive choices using a questionnaire handed out to women of child-bearing age with a confirmed diagnosis of XLHED.

Subjects and methods

Subjects

Women of child-bearing age (18–49 years) with a confirmed diagnosis of XLHED were enrolled in the study if their data had been included in a registry of patients with XLHED at the Center for Ectodermal Dysplasias in Erlangen. Chronic mental disease and acute psychological stress were exclusion criteria.

Methods

For this retrospective study, a detailed questionnaire with 75 specific questions in six sections was compiled, addressing personal data, severity of symptoms, family planning, previous pregnancies, children with XLHED, and a thought experiment, in which study participants were asked to imagine they were pregnant, and that their unborn child was affected by XLHED (questionnaire: Appendix S1). Most questions were multiple-choice items with four alternatives ranging from 'not at all' to 'very much'; for data analyses, these options were coded as numerical values from 0 to 3.

Between 1 April 2019 and 31 March 2020, the questionnaire and the documents for obtaining consent were sent out to 100 women whose data had been included in the Registry of XLHED patients of child-bearing age for a prospective clinical study, which has been kept in Erlangen since 2009. For anonymization, returned questionnaires were assigned a letter code.

Statistical analysis

Two-tailed *P*-values were calculated using Fisher's exact test or Chi-square test and considered as significant if they were <0.05.

Results

Description of the study population

Fifty women with X-linked hypohidrotic ectodermal dysplasia aged 19–49 years (mean age: 36.1 years, median age: 36 years, 1st quartile: 32 years, 3rd quartile: 42 years) participated in the study. Eleven of these women had never been pregnant, and the remaining 39 reported to have been pregnant at least once: Nine women indicated one previous pregnancy, 17 women two and 13 women more than two pregnancies. One woman was pregnant when she completed the questionnaire. Twelve subjects had a history of miscarriage, stillbirth or abortion. All 39 women with previous pregnancies reported to have at least one child, and 35 of these to have at least one child affected by XLHED. A total of 35 participants had other family members with XLHED.

Extent of XLHED symptoms

All participants were asked to indicate to what degree they were affected by XLHED symptoms and to what extent XLHED caused psychosocial problems. 38% of the women were affected by overheating and 28% by respiratory problems. Skin problems and sparse hair growth were reported by 64% and 50% of the study participants, respectively (Fig. 1). 50% of the subjects indicated an effect of XLHED on psychological well-being; approximately 30% had experienced bullying or felt confined in executing sports due to XLHED. More than 10% of the study participants reported XLHED-related problems in partnership, professional life or their relationship to family members and friends (Fig. 1). Thus, XLHED could affect all aspects of psychosocial life and well-being, at least in a minority of the study participants.

Study participants were also asked to indicate the severity of XLHED symptoms in their affected children. This part of the questionnaire was completed for 45 children with XLHED (8 girls and 37 boys). Study participants assessed XLHED symptoms of their daughters to be similar to what they experienced themselves, reporting that these girls were suffering to some extent from overheating (12.5%), dry eyes (50%), respiratory problems (37.5%), dry skin (75%) and sparse hair (87.5%), respectively (Fig. 1). XLHED symptoms of affected sons, however, were considered to be more severe than those of the study participants themselves: the mothers reported for their sons a high frequency of overheating (89.2%), dry eyes (70.3%), respiratory problems (70.3%), dry skin (83.8%) and sparse hair (81.1%).

Family planning

Several questions addressed family planning in women with XLHED. Whereas almost all women (48 out of 50) felt sufficiently informed about prenatal diagnostic and therapeutic options for XLHED, approximately one-third of the study participants (16 out of 50) prevented a pregnancy because of the risk to pass XLHED to their children. 30% of the women indicated to consider undergoing *in vitro* fertilization (IVF) with pre-implantation genetic diagnosis (PIGD) to prevent XLHED in their children (Table 1).

Thought experiment: imagined pregnancy

When asked to imagine being pregnant, all except one woman reported to be interested in prenatal diagnostics with respect to

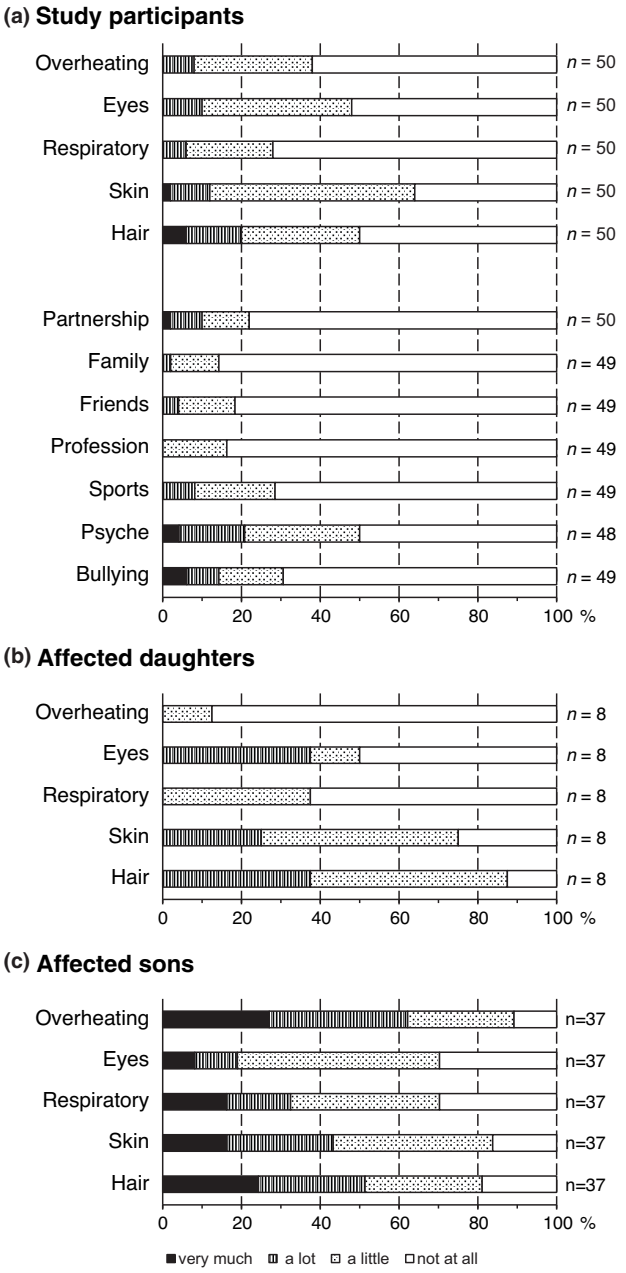

Figure 1 Severity of XLHED symptoms in study participants and their children, as evaluated by study participants. Bars represent fraction of study participants reporting to be affected very much, a lot, a little or not at all in the respective category (a), or respective reports for their daughters (b) or sons (c) with XLHED. Influence of XLHED on psychosocial well-being is also indicated. Number of women reporting or number of children being reported on is indicated on the right.

XLHED, but only 36 out of 50 study participants were interested in prenatal diagnostics addressing other diseases than XLHED. A majority of the subjects (42 out of 49) was willing to undergo invasive diagnostics. Thirteen women indicated that a prenatal diagnosis of XLHED would have an influence on continuation of the pregnancy; their mean age did not differ significantly from the mean age of women reporting that a prenatal XLHED would not have an influence on continuation of the pregnancy (36.4 *vs.* 35.2 years). In the women reporting an influence of prenatal XLHED diagnosis, there were significantly less mothers of a child affected by XLHED than in those answering 'no' to this question (7 out of 13 vs. 7 out of 37; $P < 0.05$). Nine out of 48 women would consider an abortion in case of an affected boy, or independently of the child's sex (Fig. 2a). With one exception, the study participants reported interest in a prenatal therapeutic option potentially improving the ability to sweat (Table 1).

Previous pregnancies with children affected by XLHED

Thirty-five subjects indicated to have at least one child with XLHED, and 13 of them had two or more affected children. A prenatal diagnosis of XLHED was established in 17% of cases when the pregnancy was the first with a child affected by XLHED, and in 77% of cases, when it was the second or multiplicate pregnancy with an affected child (Table 1). 50% of the women felt a moral conflict caused by the prenatal diagnosis of XLHED, 3 out of 6 women when it was the first pregnancy with an affected child, and 5 out of 10 women reporting previous pregnancies with affected children. With one exception during the first pregnancy, expectant mothers had felt sufficiently informed about XLHED.

Circumstances with potential influence on continuation of the pregnancy after a prenatal diagnosis were addressed by several items in the questionnaire. Pregnancy counselling was only mentioned once to have had an influence, whereas encounters with other persons affected by XLHED had impact on continuation of the pregnancy in 1 out of 6 cases when it was the first pregnancy with an affected child and in 5 out of 10 cases when it was the second or further child. An assumed health hazard in case of continuation of the pregnancy was only reported by one female. All women who had faced a prenatal diagnosis of XLHED would encourage other mothers of an affected fetus to continue the pregnancy (Table 1).

Three women reported previous abortions of fetuses with XLHED. Two of these fetuses were male; in one case, the fetal sex had not been determined. Two of the three women with a history of abortion had felt a moral conflict in the respective pregnancy; none of them reported that the intensity of their own XLHED symptoms had had an effect on their decision to terminate the pregnancy. The following circumstances were indicated to have an effect on the decision to undergo abortion (by one woman each): previous psychological problems, intensity of XLHED symptoms in family members, uncertainty about intensity of XLHED symptoms and lack of a therapeutic option.

Table 1 Family planning, thought experiment and previous pregnancies in women with ED

Question #		# of women		
		Yes	No	Total
Family planning				
3.1	Prevention of pregnancy because of the risk to pass on ED	16	34	50
3.2	Sufficient information on prenatal diagnostic options for ED	48	2	50
3.3	Sufficient information on prenatal treatment options for ED	48	2	50
3.4	Consideration of IVF with PIGD to prevent ED	15	35	50
3.5	Influence of prenatal treatment option on family planning	14	36	50
Thought experiment: imagined pregnancy				
4.1	Interest in pregnancy counselling	40	10	50
4.2	Interest in prenatal diagnostics with respect to ED	49	1	50
4.3	Interest in prenatal diagnostics independently of ED	36	14	50
4.4	Willingness to undergo invasive diagnostic means	42	7	49
4.5	Influence of diagnosis of ED on continuation of pregnancy	13	37	50
4.6	Acquisition of information on internet	47	3	50
4.7	Consideration of abortion in case of affected boy	9	39	48
4.8	Consideration of abortion independently of the child's sex	9	39	48
4.9	Interest in prenatal therapeutic option potentially improving the ability to sweat	47	1	48
4.10	Influence of prenatal treatment option on decision to undergo abortion	11	36	47
First previous pregnancy with child affected by ED (*n* = 35)				
5.1.1	Prenatal diagnosis of ED	6	29	35
5.1.2	Moral conflict caused by prenatal ED diagnosis	3	3	6
5.1.3	Influence of pregnancy counselling on decision to continue pregnancy	0	6	6
5.1.4	Sufficient information on ED	5	1	6
5.1.5	Influence of encountering persons affected by ED on continuation of pregnancy	1	5	6
5.1.6	Health hazard in case of continued pregnancy	1	5	6
5.1.7	Encouragement of other women to continue pregnancy with child affected by ED	6	0	6
Second or multiplicate previous pregnancy with child affected by ED (*n* = 13)				
5.2.1	Prenatal diagnosis of ED	10	3	13
5.2.2	Moral conflict caused by prenatal ED diagnosis	5	5	10
5.2.3	Influence of pregnancy counselling on decision to continue pregnancy	1	9	10
5.2.4	Sufficient information on ED	10	0	10
5.2.5	Influence of encountering persons affected by ED on continuation of pregnancy	5	5	10
5.2.6	Health hazard in case of continued pregnancy	0	10	10
5.2.7	Encouragement of other women to continue pregnancy with child affected by ED	10	0	10
Previous abortions of fetuses affected by ED (*n* = 3)				
5.2.2	Moral conflict caused by prenatal ED diagnosis in respective pregnancies	2	1	3
5.1.8/5.2.8	Fetal sex male	2	*	*
5.1.9/5.2.9	Influence of intensity of own ED symptoms on decision	0	3	3
5.1.10/5.2.10	Influence of previous psychological problems on decision	1	2	3
5.1.11/5.2.11	Influence of intensity of family members' ED symptoms on decision	1	2	3
5.1.12/5.2.12	Influence of uncertainty about intensity of ED symptoms on decision	1	2	3
5.1.13/5.2.13	Influence of lacking therapeutic options on decision	1	2	3

'Yes' refers to answer options 'very much', 'a lot' and 'a little'; 'no' refers to answer option 'not at all'.
*Sex of one child was not determined.

Influence of own children with XLHED on family planning

To determine whether having a child or several children with XLHED had an influence on reproductive decision-making, answers to respective items of the 15 women without a child affected by XLHED were compared to those of the 35 women with at least one child affected by XLHED. Almost all women were interested in prenatal diagnostics with respect to XLHED; there was no difference between women with and without a child affected by XLHED. The proportion of women preventing a pregnancy because of the risk to pass on XLHED was higher among women without an affected child, but this difference was not significant. Similar results were obtained for the items

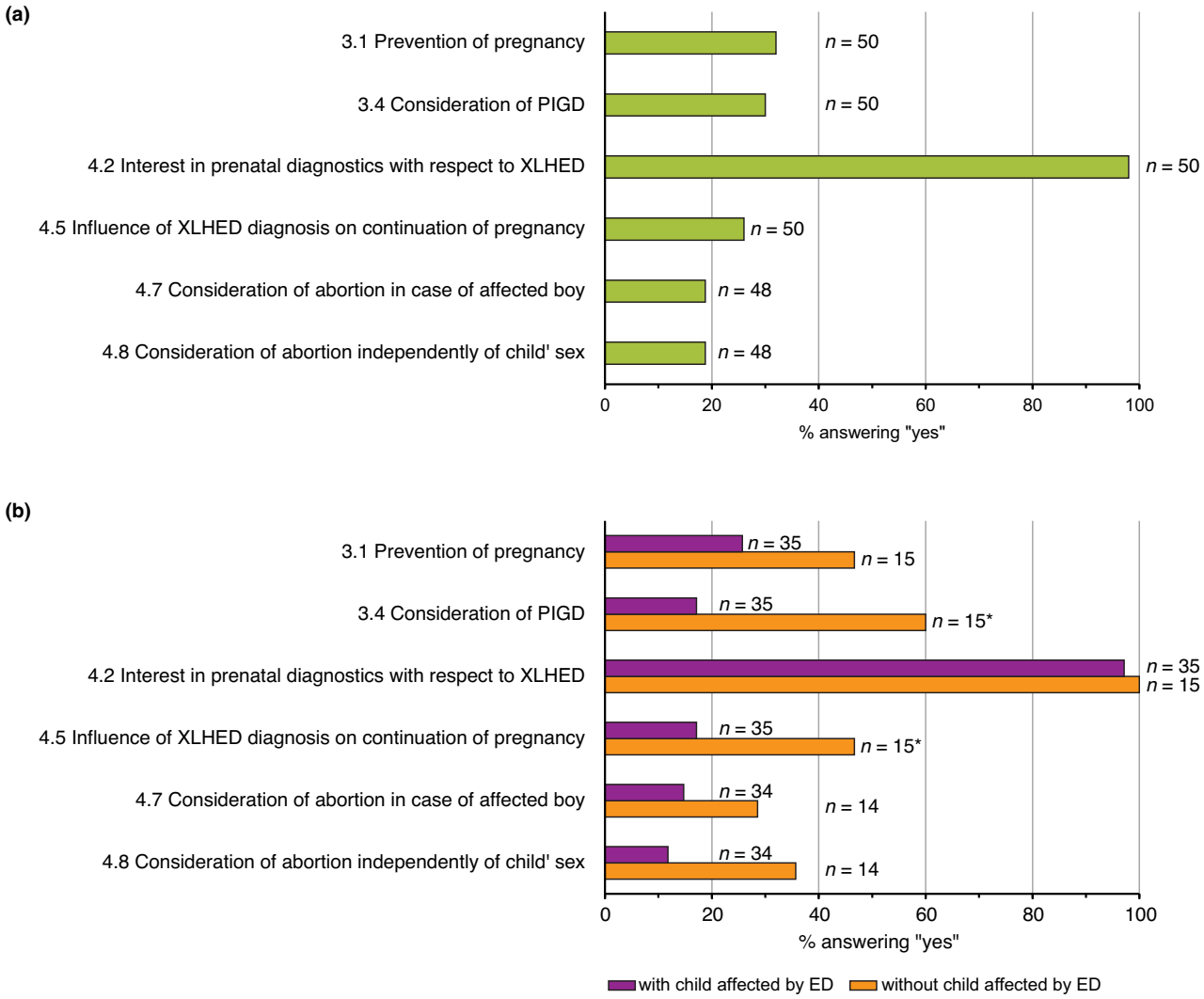

Figure 2 Influence of XLHED on family planning and on decisions in an imagined pregnancy. Fraction of women answering 'yes' for the respective items is displayed for the whole cohort (a) and for a comparison of women with or without an affected child (b). In the comparison, items with a significant difference between the two groups are marked with an asterisk.

inquiring about consideration of an abortion in case of an affected boy or independently of the child's sex. Among women with a child affected by XLHED, significantly fewer considered PIGD to prevent this disease, and significantly fewer study participants indicated that a prenatal diagnosis of XLHED would have an influence on continuation of pregnancy ($P < 0.05$; Fig. 2b).

To determine the impact of a prenatal treatment option, the respective items in questionnaires from study participants indicating an effect of XLHED on their reproductive decision-making were analysed further. A total of 16 women indicated that they would prevent a pregnancy because of the risk to pass on XLHED (Table 1, question 3.1). Eleven of them stated that a prenatal treatment option would have an impact on their family planning (question 3.5). For study participants reporting that they would consider PIGD to prevent XLHED (question 3.4), the fraction of individuals indicating that a prenatal treatment option would affect family planning was even greater; 12 out of 15 women answered 'yes' to both items. In the thought experiment, 13 women indicated that a prenatal diagnosis of XLHED would have an influence on continuation of pregnancy (Table 1, question 4.5); for six of them, a prenatal treatment option would influence the decision to undergo abortion (question 4.10). One of the three women with a previous abortion of a child with XLHED reported that the lack of a prenatal treatment option had affected their decision to terminate the pregnancy

(questions 5.1.8/5.2.8 and 5.1.13/5.2.13; Table 2). Thus, a prenatal treatment option for XLHED would have impact on family planning and reproductive decision-making in a substantial proportion of women who reported an effect of XLHED on their family planning and reproductive decision-making.

Discussion

This study shows a clear influence of the XLHED carrier state on reproductive decision-making in women of child-bearing age. Approximately, one-third of them prevents pregnancies because of the risk to pass the condition to their children. Avoiding such risk is not uncommon in carriers of genetic disease. In an American study, the majority of parents of children affected by a genetic disability or disease felt ambivalent towards having another child, and many of them tended to avoid having more children.[22] In other X-linked conditions with a more severe phenotype in affected males, for example, Duchenne's muscular dystrophy (DMD), carrier women with affected male relatives show altered reproductive behaviour and tend to avoid having affected male children themselves.[23]

Heterozygous females are usually not as severely affected by XLHED as hemizygous males. A high degree of inter- and intrafamilial variability of symptoms among affected females has been observed.[24] Females are sometimes only recognized to be carriers of XLHED when they have siblings with the condition.[25] Sons of female carriers—if affected—are likely to show a more severe phenotype than their mothers.[8] This is reflected by the finding of this study that mothers considered their sons, but not their daughters, to have more severe XLHED symptoms than they had themselves.

Although XLHED symptoms are more variable and often less severe in affected females than in males, the risk to pass the condition to their children is identical. Reproduction and family planning are important aspects of psychosocial well-being. Parents of boys with XLHED may feel guilt to have transmitted the condition to their child. In this respect, female carriers of XLHED are similarly affected as male individuals with XLHED. The women who participated in our study experienced their children's XLHED symptoms as more severe than their own, possibly explaining why a substantial number of them avoided pregnancy or considered PIGD.

Moreover, 12 women of our cohort had a history of stillbirth, miscarriage or abortion. Three subjects reported abortion of an affected child, while the percentage of women with loss of pregnancy corresponds to miscarriage rates in the general population.

On the contrary, having a child with XLHED significantly decreased the proportion of women considering PIGD to prevent XLHED, and significantly fewer women with affected children reported an influence of XLHED on continuation of an imagined pregnancy in the thought experiment. Thus, personal experience with an affected child favoured the decision for having further affected children. This group of women would also encourage other females to continue a pregnancy with a fetus diagnosed to have XLHED. In other X-linked conditions, Lesch–Nyhan syndrome and DMD, women with personal experiences of the disease in family members were more likely to avoid having affected sons,[22] which might be explained by the progressive course of disease in both conditions.

Whereas participants in the above-mentioned American study also felt ambivalent towards prenatal testing,[22] here nearly all women reported to be interested in prenatal diagnostics with respect to XLHED. This may be supported by the possibility of establishing a prenatal diagnosis non-invasively *via* sonographic tooth germ counting. For sickle cell disease, the predicted uptake of non-invasive prenatal testing was more than 90%, as opposed to an uptake of 63% for invasive tests.[26] Non-invasive means to establish a prenatal diagnosis of a genetic condition bear the danger of putting affected individuals under pressure to undergo testing, even if they are reluctant to do so. Prenatal diagnosis of XLHED may cause a conflict that puts a strain on pregnant women, or it may persuade the woman to undergo abortion of an affected fetus. Not only with the emerging non-invasive prenatal testing for genetic conditions, patient organizations and

Table 2 Influence of a prenatal treatment option on family planning and reproductive decision-making

	Family planning			**Imagined pregnancy**		**Previous abortions**	
Item		Prevention of pregnancy because of risk to pass on ED	Consideration of IVF with PIGD to prevent ED		Influence of the diagnosis of ED on continuation of pregnancy		Previous abortions of fetuses affected by ED
	Women answering 'yes'	16	15	Women answering 'yes'	13	Women answering 'yes'	3
Responses of women answering 'yes' to the item above	Influence of a prenatal treatment option on family planning			Influence of a prenatal treatment option on decision to undergo abortion		Influence of the lack of therapeutic options on decision	
	Yes	11	12	Yes	6	Yes	1
	No	5	3	No	7	No	2

parents—more than health care professionals—fear that a prenatal diagnosis will favour the selection of non-affected fetuses and lead to discrimination of individuals with genetic conditions or impairments.[27,28]

In this study, the proportion of cases in which XLHED was diagnosed prenatally rose from first to second pregnancies with affected children, but the fraction of women reporting a moral conflict after this prenatal diagnosis remained the same in first and multiplicate pregnancies. XLHED carriers seek prenatal testing for the condition if their carrier status is known, but establishment of the diagnosis still causes a moral conflict in half of the cases, and thus in a substantial number of women. Such consequences should be thoroughly discussed with XLHED carriers of child-bearing age. Also, as recommended for other X-linked diseases, professional counselling of girls or women affected by XLHED should explicitly include addressing the carrier state rather than leaving this aspect to the families.[29]

Once a child is born, screening for disease, as performed in newborn screening, is considered to be justified if there is an effective intervention to alter the natural history of the condition.[30] In XLHED, early diagnosis of the disease improves prognosis, because life-threatening overheating in early infancy can be avoided by awareness of insufficient thermoregulation in affected infants.[18,19] This may explain why affected women are favourable of establishing a diagnosis of XLHED in their children as early as possible, and thus prenatally. Although in most cases a prenatal diagnosis does not have direct therapeutic consequences, a therapeutic option potentially available for XLHED in the future[20] may change this paradigm and shape reproductive decision-making in affected families. Here, many women avoiding pregnancy because of their XLHED carrier state or considering assisted reproduction by means of PIGD have reported an influence of such a therapeutic option on family planning, and the current lack of therapeutic options was indicated to result in decisions to terminate an affected pregnancy.

Family planning and reproductive decision-making are altered in XLHED carriers. Most women seek prenatal diagnosis, which does not alleviate the moral conflicts many XLHED carriers feel when they are pregnant. A prenatal treatment option would have a strong influence on reproductive decisions, underlining the importance of adequate professional counselling of affected girls and women of child-bearing age and showing the impact of prenatal treatment options on reproductive decision-making in genetic disease.

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Ethics approval and consent to participate

Written informed consent was obtained from all study participants. The study was approved by the ethics committee of the Friedrich–Alexander University Erlangen–Nürnberg and was conducted in compliance with all national legal requirements.

Data availability statement

Availability of data and materials. The datasets used and analyzed during the study are available from the corresponding author upon reasonable request.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1: Questionnaire: Reproductive decision-making and potential conflict during a pregnancy in women with X-linked hypohidrotic ectodermal dysplasia.