



# Beyond hormone replacement: quality of life in women with congenital hypogonadotropic hypogonadism

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## Abstract

**Objective:** Little is known about how women with isolated GnRH deficiency cope with their condition. This study aimed to examine the health and informational needs of women with congenital hypogonadotropic hypogonadism (CHH) and evaluate if their experiences differ from women with more common forms of infertility.

**Design:** Cross-sectional, multiple methods study using web-based data collection to reach dispersed rare disease patients.

**Methods:** A community-based participatory research framework was employed to develop an online survey and collect quantitative and qualitative data. Adult women diagnosed with CHH who had received at least one year of hormonal treatment completed the Morisky Medication Adherence Scale, Revised Illness Perception Questionnaire and Zung Self-Rating Depression Scale. Information on health care experiences, treatment outcomes and patient-reported challenges were also collected.  
**Results:** Women ( $n = 55$ ) were often diagnosed late ( $20.7 \pm 7.4$ , range: 10–48 years) and 16/20 patients receiving fertility treatment conceived. Poor adherence was frequently observed (34/55) while more than half (27/49) reported a gap in treatment exceeding a year. Low adherence correlated with depressive symptoms ( $r = 0.3$ ,  $P > 0.05$ ). Negative illness perceptions were pervasive and 30/55 exhibited some depressive symptoms – significantly greater than women with common female factor infertility ( $P < 0.01$ ). Symptoms were underappreciated by providers as only 15 of 55 patients had discussions about psychological services. Women identified isolation, need for information and finding expert care as challenges to living with CHH.

**Conclusions:** Despite being a treatable form of female infertility, the presumable availability of treatment does not necessarily ensure adequate quality of life for women with isolated GnRH deficiency.

## Key Words

- ▶ female infertility
- ▶ illness perceptions
- ▶ Kallmann syndrome
- ▶ medication adherence
- ▶ patient-centered care
- ▶ rare diseases

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## Introduction

Infertility affects ~10–15% of women globally and is a significant health concern (1). Sometimes referred to as the pilot light of reproduction, gonadotropin-releasing hormone (GnRH) secretion is essential for developing and maintaining the reproductive capacity (2). Acquired GnRH deficiency (i.e. hypothalamic amenorrhea) is a common cause of secondary amenorrhea that is reversible (3). More severe forms of GnRH deficiency, such as congenital hypogonadotropic hypogonadism (CHH), are much less common. However, CHH is responsive to hormonal therapy and is a treatable form of infertility that does not necessarily require invasive assisted reproduction techniques (4).

In its most severe form, CHH presents as a complete absence of puberty with undetectable serum gonadotropins and hypogonadal sex steroid levels. Clinical presentation is variable: some patients display partial puberty (5), there is a wide range of associated phenotypes (e.g. absent sense of smell, skeletal anomalies, mirror movements, renal agenesis) and cases of reversal have been reported (6). Similarly, genetic etiology is heterogeneous with more than 25 genes having been identified in relation to CHH and the genetic architecture can sometimes be complex as evidenced by oligogenicity (4). CHH is rare (1:4000–10,000) and there is a striking sexual discordance. Combining three large patient cohorts from the United States ( $n=250$ ) (7), United Kingdom ( $n=215$ ) (8) and France ( $n=334$ ) (9) reveals the male to female ratio to be 3.6–1. Yet, unlike many other rare disorders, effective treatments are available. Hormone replacement in the form of low-dose estradiol (titrated over time) is the standard treatment for younger hypogonadal women to induce secondary sexual characteristics and menses (4). Combined gonadotropin therapy or physiologic treatment with pulsatile GnRH are equally effective for inducing fertility in the vast majority of cases (10).

Compared to fertile counterparts, women with infertility have higher levels of stress, anxiety and depression, and all of which can erode the quality of life (11). However, little is known about the experiences of women with CHH and how they cope with their condition. There is a body of literature on quality of life issues in women with primary infertility (i.e. Turner syndrome, TS) (12). However, differences in terms of timing of diagnosis, phenotype and fertility potential preclude extending findings from women with a hypogonadotropic cause of infertility (TS) to those with a hypogonadotropic etiology (CHH). Notably, conducting research in rare disease

patients is challenged by the fact that these patients are dispersed and difficult to reach. Therefore, the purpose of this study was to partner with patients and use web-based data collection to reach women with CHH to conduct a needs assessment to identify targets for developing more patient-centered approaches to care for these endocrine patients.

## Subjects and methods

### Design and subjects

This cross-sectional needs assessment employed multiple methods within a community-based participatory research framework (13). We engaged patient community leaders in developing content and validating the online survey as well as for recruitment. Patients were identified via patient-oriented social media sites (i.e. Facebook, Rareconnect.org) and the international network studying GnRH deficiency (COST Action BM1105, [www.gnrhdeficiency.eu](http://www.gnrhdeficiency.eu)) over a 14-month period (October 2014–December 2015). CHH was defined as previously reported (5) and diagnosis was confirmed in a 40% random sample of respondents as described (14). Adult women (18+ years) with CHH who had been on hormonal treatment for at least one year were included in the analysis. The project was reviewed and approved by the local ethics committee, and all participants provided opt-in electronic consent.

### Needs assessment survey

We co-constructed an online survey with patients including items on patient demographics, health literacy (15), medical history, health care interactions, sexuality as well as several validated questionnaires. The selection of questionnaires was based on their relevance, validity and widespread use that facilitate comparison with particular patient populations of interest (i.e. women with infertility and men with CHH and patients with rare endocrine disorders and chronic conditions). The Morisky Medication Adherence Scale (MMAS) is an 8-item instrument that assesses medication taking behavior to determine low, medium or high adherence (16, 17, 18). The Zung Self-Rating Depression Scale (SDS) is a widely used, validated 20-item instrument quantifying the severity of affective, somatic, psychomotor and psychological depressive symptoms (19, 20). The Illness Perception



Questionnaire – Revised (IPQ-R) includes 38 statements to assess emotional and cognitive representations of illness spanning 7 dimensions: *timeline acute/chronic* (beliefs about the chronic nature of the condition), *timeline cyclical* (beliefs regarding the cyclical nature of the condition), *consequences* (negative consequences of the disease), *personal control* (perceived personal controllability of the disease), *treatment control* (perceived treatment controllability of the disease), *emotional representations* (the emotional responses generated by the illness) and *illness coherence* (personal understanding of the disease) (21). Additionally, patients had the opportunity to provide a free text response identifying what they perceive to be the most challenging aspects of living with CHH.

### Reference populations

To provide context for the depressive symptoms in women with CHH, SDS scores were compared to: (a) men with CHH ( $n=101$ ) (22), (b) women seeking assisted fertility treatment ( $n=872$ ) (11) and (c) community-based rates in a healthy, non-psychiatric population ( $n=292$ ) who completed the SDS monthly over the course of one full year (23). Because there are no normative scores for the IPQ-R for the general population (i.e. healthy adults), comparisons were made to patients with acute or chronic pain (24), men with CHH (22) and patients with acromegaly (24) to provide a clinical context for these data. Age at CHH diagnosis was compared to a population-based sample for age of menarche (25).

### Analysis

Descriptive statistics were used to present survey data. Comparisons between groups were performed using Student's *t*-test or Mann–Whitney rank-sum test as appropriate. Categorical values were compared using chi-square test while Pearson product–moment correlations were performed to assess the associations between survey data. IPQ-R subscales were compared across the CHH and reference groups using ANOVA with Bonferroni post hoc correction for multiple comparisons. *Z*-scores were used to assess the differences in the proportion of patients exhibiting depressive symptoms compared to community base rates. Survey data were analyzed using PASW Statistics, version 17.0.2 (SPSS Inc., Chicago, IL). All data are presented as mean  $\pm$  s.d. unless otherwise noted and a  $P \leq 0.05$  was considered statistically significant. Open-ended responses were analyzed using NVivo11

(QSR International PSY Ltd., Melbourne Australia). Deductive thematic analysis (deductive coding) was conducted by two independent investigators (SD and AD). Meaningful units were coded. These codes were sorted into categories and themes in an iterative process and consensus was achieved by discussion. The most frequent themes were given particular emphasis (26).

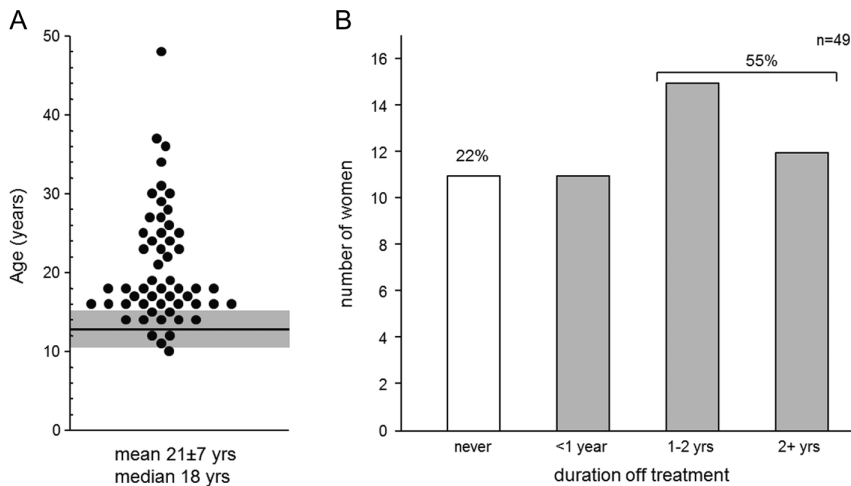
## Results

The web-based survey was online for 14 months during which time 68 women responded. After removing incomplete survey responses and those not meeting inclusion criteria, 55 surveys were included for analysis. Given the rarity of women with CHH (7, 8, 9), it appears that the combination of community partnerships and social media recruitment were effective for reaching these dispersed patients (14). Patient sociodemographic characteristics are depicted in Table 1. The women ranged in age from 18 to 68 years (mean  $35 \pm 10$ , median 34), were well-educated (44/55, university or higher) with adequate health literacy and the majority of women were employed (41/55).

**Table 1** Sociodemographic information of women with CHH ( $n=55$ ).

	<i>n</i> (%)
<b>Age (years)</b>	
18–29	16 (29%)
30–39	25 (46%)
40–49	9 (16%)
50–59	4 (7%)
60+	1 (2%)
<b>Education</b>	
High school/vocational	10 (18%)
University	28 (51%)
Post-graduate	16 (29%)
No response	1 (2%)
<b>Health literacy (25)</b>	
Adequate literacy	45/55 (82%)
Inadequate literacy	10/55 (18%)
<b>Employment</b>	
Working full-time	32 (58%)
Working part-time	9 (16%)
Not working/unemployed	8 (15%)
Retired	1 (2%)
Student	5 (9%)
<b>Relationship status</b>	
Married	21 (38%)
In a relationship	14 (25%)
Single	9 (16%)
Never been in a relationship	4 (7%)
Divorced	7 (13%)



**Figure 1**

Age at CHH diagnosis and self-reported adherence to treatment. (A) Age at CHH diagnosis for 55 women ranged from 10 to 48 years. The mean age at menarche for Caucasian females is shown as a horizontal line, and the shaded region depicts  $\pm$  two s.d. (36). Only 11/55 women were diagnosed by age 15 years. (B) Self-reported adherence to treatment ( $n=49$ ). Approximately one-quarter of respondents reported never having a gap in treatment. In total, more than half (27/49) reported a gap in treatment of a year or longer. Similarly 20/46 women reported having a lapse in health care exceeding one year (data not shown). Age at diagnosis was moderately correlated with duration of gap in health care ( $r=0.56$ ,  $P<0.001$ ).

Given that menarche is an important single-event signpost of puberty and that 90% of CHH women present with primary amenorrhea (5), earlier diagnosis and treatment would be expected compared to male counterparts who lack such a hallmark. However, we found no such pattern (females:  $n=55$ ; 95% CI: 18.7–22.7, males:  $n=101$ ; 17.6–20.2 years;  $P=0.16$ ) (22). The women were diagnosed between 10 and 48 years of age (Fig. 1A), and more than half ( $n=32$ ) had received any meaningful treatment prior to age 18 years (95% CI: 17.2–20.6 years). Nearly two-thirds (34/55) of survey respondents had been seen at a specialized academic medical center (Table 2). Twenty women underwent fertility-inducing treatment, two-thirds (13/20) of whom at an academic medical center and the vast majority (16/20) successfully conceived, consistent with rates previously reported (27, 28), and in line with male CHH counterparts (95% CI: 60–85%) (29). In total, nearly half (25/55) the women had undergone genetic testing yet significantly fewer (11/55,  $P<0.005$ ) received genetic counseling. Among surveyed patients, women receiving fertility-inducing treatment were not more likely to have genetic testing (12/20,  $P=0.10$ ) or counseling (5/20,  $P=0.48$ ) compared to the larger group.

All respondents included in the analysis had been on treatment for at least one year. Women completed the MMAS to assess adherence behavior (Table 2) and provided self-reported longest duration off treatment (Fig. 1B). Notably, MMAS scores indicated low adherence in nearly two-thirds (34/55) of women. Lifetime duration of treatment was weakly correlated with MMAS ( $r=0.29$ ,  $P<0.05$ ). Only 11/49 reported never having a lapse in treatment – a proportion similar to those exhibiting the highest level of adherence on the MMAS (Table 1). However, more than half (27/49) reported long gaps in

treatment (i.e. 12 months or longer). Similarly, 18/43 claimed to have gone 2 years or longer without seeing a health care provider (data not shown).

Across IPQ-R dimensions, women and men had comparable perceptions of their CHH with scores indicating significant emotional impact and negative consequences (22) (Table 3). These findings extend the findings of a small qualitative study including interviews with 5 women with

**Table 2** Health care experiences of women with CHH ( $n=55$ ).

	n (%)
<b>Medical history</b>	
Seen at a specialized academic medical center	34 (62%)
Genetic testing performed	25 (45%)
Genetic counseling received	11 (20%)
Sought psychological counseling	16 (29%)
<b>Health care interactions</b>	
Provider understands medical aspects of CHH	28 (51%)
Provider understands patient's feelings of living with CHH	14 (25%)
Provider discussed or gave referral for counseling	15 (27%)
Experienced discrimination in the health care system	15 (27%)
<b>Treatment and adherence</b>	
Duration of treatment: mean $\pm$ s.d. (range, median)	16 $\pm$ 10 years (1–42, 17)
MMAS low adherence	34 (62%)
MMAS medium adherence	12 (22%)
MMAS high adherence	9 (16%)
<b>Fertility outcomes</b>	
Received fertility-inducing treatment	20/55 (36%)
Biologic children	16/20 (80%)

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**Table 3** Comparison of IPQ-R scores between female CHH patients and other patient groups.

IPQ-R	CHH (women) (n=55)	CHH (men) (n=101)	acute pain (n=35)	chronic pain (n=63)	Acromegaly (n=81)
Timeline (acute/chronic)	<b>27.2 (3.6)</b>	26.7 (3)	13.4 (5)**	23.1 (4)**	22.9 (6)**
Timeline (cyclical)	<b>9.2 (3.9)</b>	9.7 (4)	9.4 (3)	12.9 (4)**	10.1 (4)
Consequences	<b>20.0 (5.1)</b>	21.3 (4)	14.2 (4)**	23.5 (4)**	16.9 (5)**
Emotional representations	<b>17.8 (6.2)</b>	19.2 (6)	16.1 (4)	19.8 (4)	12.6 (4)**
Personal control	<b>19.6 (4.9)</b>	19.9 (5)	22.9 (4)**	18.4 (4)	17.5 (5)
Treatment control	<b>16.1 (3.3)</b>	15.5 (4)	19.4 (3)**	14.2 (3)*	18.1 (3)**
Illness coherence	<b>16.5 (4.7)</b>	18.1 (4)	9.3 (3)**	13.4 (5)**	17.5 (3)

Data are mean (s.d.), \* $P < 0.05$  compared with CHH (women), \*\* $P < 0.01$  compared with CHH (women).

CHH (30). Women with CHH perceived more negative consequences of their illness compared to both patients with acute pain and patients with acromegaly (both  $P < 0.01$ ) yet less than patients with chronic pain. The negative emotional impact of CHH was larger than that in patients with acromegaly ( $P < 0.01$ ) but not different from patients with acute or chronic pain. Both negative consequences and emotional impact were modestly correlated with poorer medication adherence ( $r = 0.298$  and  $r = 0.33$  respectively, both  $P < 0.05$ ). Furthermore, females with CHH perceived less personal control over their illness than patients with acute pain ( $P < 0.01$ ), but did not differ from patients with chronic pain or acromegaly. In terms of treatment control, females with CHH perceived less treatment control than patients with acute pain or acromegaly (both  $P < 0.01$ ), but more treatment control than patients with chronic pain ( $P = 0.01$ ). Lastly, women with CHH exhibited the highest score on illness coherence compared to patients with acute or chronic pain (both  $P < 0.01$ ). This better understanding of their illness could be related to the congenital nature of CHH.

More than half the women (30/55) exhibited some depressive symptoms. This is significantly increased compared to the 9% observed in a community dwelling non-psychiatric population ( $P < 0.001$ ) (23) yet similar to their male CHH counterparts (64/100,  $P = \text{N.S.}$ ) (22). Compared to those presenting with more common female infertility (14.7% of 872 women) (11), women with CHH were more likely to exhibit depressive symptoms ( $P < 0.01$ ), and this relationship persisted when we limited the analysis to only those patients (25.6% of 193 women) with female factor infertility ( $P < 0.01$ ). In total, 14/55 women with CHH exhibited mild depressive symptoms, 9/55 had moderated symptoms similar to the type of depression treated in an ambulatory setting while 7/55 had severe depressive symptoms akin to major depressive disorder. We found depressive symptoms were moderately correlated with poorer medication adherence ( $r = 0.3$ ,  $P < 0.05$ ) consistent with prior studies in patients with chronic

diseases (31). Depressive symptoms were also correlated with illness perception dimensions. We observed a strong correlation between depressive symptoms and negative emotional impact of CHH ( $r = 0.6$ ,  $P < 0.0001$ ), a moderate relationship with consequences ( $r = 0.42$ ,  $P < 0.01$ ) and a weak association with illness coherence – how one makes sense of their condition ( $r = 0.35$ ,  $P < 0.01$ ).

Importantly, the increased depressive symptoms appear to be underappreciated as only 15 women stated that their provider had discussed or provided a referral for psychological counseling. Half the patients (28/55) perceived that their health care provider well understood the medical aspects of their GnRH deficiency yet significantly fewer felt that their provider understood how patients feel about living with CHH (14/55,  $P < 0.01$ ). Women with CHH were more likely than their male counterparts to have been in a relationship and sexually active (both,  $P < 0.05$ ) (32). Despite this, nearly all women (51/55) cited issues of body image concerns, with 44/55 reporting feelings of shame or embarrassment about their body and over half (32/55) found intimate relationships difficult and had experienced teasing or ridicule about their lack of development (31/55).

Qualitative data were also collected as part of the survey. Patients were asked to describe the most challenging aspect of living with CHH and approximately two-thirds (36/55) responded. Responses were coded and the 61 topics thematically clustered in three categories: (i) isolation and insecurity ( $n = 24$ ), (ii) need for information and support ( $n = 24$ ) and (iii) delayed diagnosis and finding expert care ( $n = 13$ ). A table with representative quotes is provided in the online [supplemental file](#) (see section on [supplementary data](#) given at the end of this article). We also asked patients where they sought information about their condition. Nearly all women (52/55) reported that they found information about their condition on the internet, 46/55 via online community and social media (i.e. Facebook, Rareconnect.org) and 44/55 were informed by health care professionals. Despite high education and

health literacy levels, approximately half (27/55) sought information from the medical literature. Patients rated health care professionals as the most important source of information followed by online community and the Internet. Ratings of importance were not statistically significant between these sources ( $P=0.13$ ).

## Discussion

We found that women with CHH are often diagnosed late and experience significant physical, social and psychological consequences in relation to their condition. These findings have implications for developing more patient-centered approaches to care for these women. This cross-sectional study of 55 women is perhaps the most robust portrayal of this patient population to date. Data on women with CHH are scant with only a handful of single-center studies reporting on very small samples (i.e.  $n<15$ ). Additionally, patients were involved in developing the study – this strengthens our confidence that the identified targets for improving care are aspects that matter to patients.

Some aspects of this study may limit the ultimate transferability of the findings to all women with CHH. First, these patients were well educated with high levels of health literacy. Second, the inherent Anglophone bias should engender caution in considering cultural equivalence. Third, given the sample size, we may be underpowered in some of our analyses. Indeed, difficulty in recruiting adequate numbers of patients with rare diseases is widely acknowledged. This challenge informed our strategy of using the Internet and patient-oriented social media to reach these dispersed patients, which we acknowledge as a potential source of sampling bias. Finally, self-report nature of the instruments employed has its own limitations, albeit our goal was to better understand patient perspectives to identify the unmet needs as an initial step in developing more patient-centered approaches to care.

Data on the age of diagnosis in CHH women comprise a single article ( $n=5$ ; mean:  $23\pm 9$ , range: 12–35, median 21 years) (30) along with some unpublished historic data (females:  $n=38$ ; mean:  $18.2\pm 5$ , range: 10–53 years) (33). We found women with CHH are often diagnosed quite late and only 58% had received treatment prior to age 18 years. It is well established that later induction of puberty for adolescent girls with TS is associated with poor self-esteem, difficult social adjustment and diminished sex life (34, 35). Further, late diagnosis (and initiation of

treatment) negatively impacts psychosexual development in men with CHH (32). Thus, greater attention to earlier detection and timely initiation of sex steroid therapy seems warranted.

The vast majority (16 of 20) of women who underwent fertility treatment were able to conceive, in line with published literature (27, 28). Notably, relatively few (11/55) women had received genetic counseling. This is surprising given that the American College of Medical Genetics considers abnormal pubertal timing a clinical presentation requiring referral to a medical genetics professional (i.e. genetic counselor) (36). Further, both the European Society of Human Genetics and the European Society of Human Reproduction and Embryology consider genetic counseling necessary when genetic factors are related to the cause of infertility (37). However, in our cohort, women receiving fertility-inducing treatment were no more likely to have genetic testing or counseling. These data suggest either lack of awareness of the importance of genetic counseling for these patients or may reflect inadequate access to specialists with sufficient understanding of the sometimes complex genetics of CHH (38). Improved access to genetic counseling appears to be a relevant target for enhancing patient care.

Long-term adherence to treatment was problematic as more than half of women had a gap in care of a year or longer. Without treatment, these women rapidly become hypogonadal, with deleterious impact on mood, well-being, sex life and bone health. A Finnish cohort of 24 men and 9 women found patients with the longest gaps in treatment exhibited the most impaired bone density (39). Additionally, risk for osteopenia/osteoporosis may be further compounded by late diagnosis, as up to 90% of adult bone mass is accumulated during adolescence (40). Delays in diagnosis (and treatment initiation) could prolong estrogen deficiency thus impairing bone mineralization. These data highlight the importance of adequate hormone replacement and ongoing follow-up to monitor bone density and adherence as well as the role for a coordinated transition to adult services to facilitate continuity of care (4, 39, 41).

Women had negative illness perceptions yet exhibited relatively high scores on illness coherence. Interestingly, CHH women who had received fertility treatment (and were able to conceive) had significantly lower ratings of negative consequences ( $P<0.05$ ) and emotional impact ( $P<0.05$ ) compared to those without children. While the sample is small, this may represent a psychological buffering effect of successful fertility treatment. We did not employ a formal health-related



quality of life (HR-QoL) instrument in this study; yet, the negative illness perceptions and increased depressive symptoms observed in women with CHH are consistent with impaired HR-QoL. A recent study of women with TS showed impaired HR-QoL compared to controls (35). Interestingly, the study included 21 women with other types of congenital hypogonadism (14 with CHH, 7 with 46XX gonadal dysgenesis) whose SF-36 scores were quite similar. A subset of these patients completed the Female Sexual Function Index revealing impaired sexual desire, arousal, lubrication, orgasm and global satisfaction compared to controls (35). Similarly in our cohort, body image concerns were pervasive and the majority of women stated that intimate relationships were difficult. A recent study of young adults with CHH during transition found that few young women felt adequately informed about sexuality (2/7), intimate relationships (1/7), potential future fertility (1/7) or intercourse/potential discomfort with sex (0/7) (42). These current data underscore the need for appropriate anticipatory guidance on the topics of sexuality and intimate relationships.

The qualitative data analysis suggests that women struggle with feelings of isolation and finding expert care. They frequently reported having used the Internet and social media to learn about their condition and to find support from other patients (14). The Pew Foundation identified patients with a rare disease as 'Internet power-users' (43), which aligns with our findings. We have previously shown that Web-based modalities are used by and acceptable to patients with CHH (14). This may present a novel avenue for reaching these dispersed patients, engaging them and promoting health and self-management. The Institute of Medicine defines patient-centered care as being guided by patient values and is both respectful of, and responsive to individual preferences, needs and values (44). The Picker Principles of patient-centered care (45) provide a useful framework for developing more patient-centered approaches to care. Accordingly, we have charted the findings from the present study onto this framework along with suggested avenues for translating the results of this study into improved care for women with CHH (see [supplemental file](#)).

In summary, this participatory, multiple methods needs assessment identifies that women with CHH frequently have lengthy gaps in treatment/care, perceive their condition to have a significant psychosocial impact on their life and exhibit increased depressive symptoms. Care for these women could be improved by earlier diagnosis and timely initiation of treatment, greater access to genetic counseling and providing accurate information

about CHH (and fertility treatment) as well as offering professional and peer-to-peer psychological support. The Internet is effective for reaching and connecting dispersed patients, and Web-based platforms may hold promise for delivering patient-centered interventions to empower patients for improved self-management and adherence.

#### Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EC-17-0095>.

#### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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#### Author contribution statement

A A D, R Q, N P and D M conceived and designed the study. A A D collected the data. S D, J T and A A D analyzed the data and drafted the manuscript. R Q, N P and D M critically revised the manuscript. All authors approved the final manuscript version.

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