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ORIGINAL ARTICLE

Gynecologic health in cartilage-hair hypoplasia: A survey of 26 adult females

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Cartilage-hair hypoplasia (CHH) is a rare metaphyseal chondrodysplasia significantly affecting adult height and quality of life. Immunodeficiency and increased risk for malignancies contribute to significant morbidity. Little is known about gynecologic health in CHH. We performed a questionnaire study of 26 women (mean age 42.3 years) with genetically confirmed CHH, inquiring about pubertal development, menstrual cycle, use of contraception, pregnancies, gynecologic infections, and gynecologic cancers. Mean age at menarche and menopause was 12.7 and 46.1 years, respectively. Mean length of menstrual cycle was 27 days. Contraception was used by 76%, most commonly condom (60%), and combined contraception (60%). Despite significant short stature (mean height 121 cm) and potentially small pelvic diameters, 10 CHH women (38%) had been pregnant. Six of these women reported miscarriages and three had, induced pregnancy terminations. Eight women had in total, 19 deliveries. Abnormal Pap smear was reported in five patients and cervical cancer once. Our findings of normal timing of puberty and menopause suggest a fairly normal length of the fertility period in women with CHH. However, many patients expressed concerns regarding the safety of pregnancy and lack of prepregnancy counseling. Immunodeficiency may predispose CHH women to prolonged HPV infections. This study highlights the importance of careful gynecologic follow-up for these patients.

KEYWORDS

CHH, contraception, fertility, pregnancy, puberty, *RMRP*, skeletal dysplasia

1 | INTRODUCTION

Cartilage-hair hypoplasia (CHH; OMIM #250250) is a rare autosomal recessive metaphyseal chondrodysplasia with an incidence of 1:23,000 births in Finland (Mäkitie, 1992; Mäkitie & Kaitila, 1993). It is characterized by severe short-limbed growth failure (mean adult height for males is 131 and 123 cm for females), thin and sparse hair, combined immunodeficiency, bone marrow failure and increased risk for Hirschsprung disease, and malignancies. CHH is caused by biallelic mutations in the noncoding RNA gene, *RMRP*. *RMRP* mutations disrupt ribosomal processing and progression through the cell cycle, which results in defective cell proliferation (Ridanpää et al., 2002). CHH is highly variable in severity with phenotypic differences also within families.

Despite the growing knowledge of disease mechanisms, many clinical aspects of the disease still remain uncharacterized. Only limited data are available regarding puberty, reproduction, and gynecologic health in patients with CHH. In a previous Finnish study from 1993 involving 15 CHH females, spontaneous menarche was reported at a mean age of 13 years, consistent with normal pubertal maturation in general population (Mäkitie & Kaitila, 1993; Parent et al., 2003). In a small American CHH cohort (n = 5), mean age at menarche was 14.2 years and menopausal age was reported by only one patient (45 years) (Allanson & Hall, 1986). In the same study three CHH women were reported to have five pregnancies, details of the pregnancies are unknown (Allanson & Hall, 1986). Recently, a case report described prenatal care and preterm delivery at 34 weeks gestation in one CHH woman (Thavarajah & Berndl, 2017). There is no previously published data on gynecologic infections or gynecologic cancers in CHH women.

Because the bone marrow and the immune system are affected in CHH, there are many potential and clinically highly relevant gynecologic problems in CHH patients, including vulnerability to gynecologic infections due to immunodeficiency; risk for heavy menstruation and consequent exacerbation of anemia due to bone marrow dysfunction; and a possibly increased risk for gynecologic malignancies. Moreover,

disproportionate short stature may cause problems in sexual life and complicate pregnancies and delivery (Apajasalo, Sintonen, Rautonen, & Kaitila, 1998).

We performed a questionnaire study of 26 adult CHH women (mean age 42.3 years) to gain knowledge on pubertal maturation, gynecologic health, contraception use, pregnancies, and menopausal age.

2 | MATERIALS AND METHODS

2.1 | Patients

This study was performed as a part of our ongoing research program on CHH. The study protocol was approved by the Institutional Review Board of the Children's Hospital, University of Helsinki and all study participants gave a written informed consent for participation. Patients were identified from the Finnish Skeletal Dysplasia Registry which includes >160 patients with genetically confirmed CHH. All *RMRP* mutations had been detected by Sanger sequencing either at Laboratory HUSLAB, Finland, or as a part of previous or ongoing research at Folkhälsan Institute of Genetics, Helsinki (Ridanpää et al., 2002; Kostjukovits, et al., 2017). Our study sample comprised CHH women over 18 years of age. The study questionnaire was sent to a total of 55 women; 26 CHH females returned the questionnaire, accounting for a response rate of 47%.

2.2 | Data

The questionnaire covered health-related issues, medication, pubertal development, menstrual cycle, cycle-related symptoms, gynecologic infections, Pap smear screening, contraception, pregnancies, menopausal symptoms, hormone replacement therapy, and gynecologic malignancies.

2.3 | Statistical analysis

Standard statistical methods were used as appropriate. Median and mean and/or standard deviation estimates were computed for variables such as age, height and weight.

3 | RESULTS

The study cohort comprised 26 women, mean age being 42.3 years (range 19.2–70.8 years). The mean height of the patients was 121 cm (range 95–150 cm), all less than −2 *SD* compared with healthy Finnish population (Mäkitie, Perheentupa, & Kaitila, 1992). Twenty-two patients were homozygous for the RMRP g.70A > G mutation. Four patients had compound heterozygous mutations (g.70A > G/g.262G > T). Detailed patient characteristics are described in Table 1.

3.1 | Age at menarche and at menopause

Of the 26 patients, 24 reported normal age of spontaneous menarche with adequate secondary sexual development (Table 2). None of the patients reported precocious puberty. In two patients, delayed puberty had been diagnosed, one of them had unexplained nonfamilial hypogonadotropic hypogonadism; the other had delayed spontaneous menarche until the age of 20 years, but developed lymphoma at the same age and premature ovarian insufficiency ensued due to cytotoxic medication. Pubertal induction was used in the first case and permanent adult-dose hormone replacement therapy in both patients.

Of the 11 women aged >45 years, eight women underwent natural menopause, and the mean age of 46.1 years (Table 2). Two women could not define their menopausal age because of previous uterine surgery. One woman (48.5 years) had still irregular cycles. Five menopausal women used hormone replacement therapy.

3.2 | Menstural cycle

The mean length of menstrual cycle and duration of menstruation were normal (Table 2). Dysmenorrhea, either current or previous, was reported in 15/25 (60%) of patients. One patient had hysterectomy before menopause and two others underwent endometrial ablation because of heavy bleeding.

3.3 | Contraception

Twenty of the 26 women had had a history of sexual intercourse. The use of previous and current contraception methods is reported in Table 3. Most women had tried several different methods, potentially reflecting difficulties finding suitable contraceptives.

3.4 | Pregnancies

Ten women (38%) had been pregnant. Most of the pregnancies were spontaneous; only one woman had received unspecified infertility treatment. Six women (23%) had a history of spontaneous abortion.

TABLE 1 Characteristics reported by the 26 adult CHH women

Age (years)	
Mean	42.3
Range	19.2–70.8
Height (cm)	
Mean	121
Range	95–150
BMI (kg/m^2)	
Mean	34.4
Range	20.7–63.1
Accompanying illnesses requiring treatment with medication, *n* (%)	
Asthma	5 (19)
Allergy	3 (12)
High blood pressure	5 (19)
Type 2 diabetes	2 (8)
Rheumatic disease	1 (4)
Migraine	1 (4)
Depression	3 (12)
Malignancy	2 (8)
Lymphoma	1 (4)
Cervical cancer	1 (4)

TABLE 2 Gynecologic characteristics reported by the 26 CHH women

Puberty	*n*	%
Normal	24	92
Delayed	2	8
Age	Mean	Range
At menarche (years)	12.7	11–16
At natural menopause (years) (*n* = 8)	46.1	40–52
Menstrual cycle length in days (*n* = 20)	Mean	Range
	27	21–60
Duration of menses	5	2–7
Menstrual bleeding (*n* = 23)	*n*	%
Mild	4	17
Moderate	16	70
Heavy	3	13

They had no history of autoimmune diseases and data on antiphospholipid antibody screening were unavailable. No stillbirths were reported. Legal induced abortion had been performed for three women. A total of eight women gave birth to 19 children, including one twin pregnancy. Caesarean section was performed in all pregnancies because of cephalopelvic disproportion or previous caesarean sections. Elective induction of labor was attempted prior to caesarean section in one case. Two women each had a history of four, and two women of each had a history of three caesarean deliveries. There were no self-reported pregnancy complications. The mean age at delivery was 29.6 years (range 22–36 years).

3.5 | Gynecologic health and concerns

Recurrent gynecologic infections were reported by 7/26 (27%) women, including recurrent candidiasis (*n* = 3), condyloma accuminata (*n* = 3) and nonspecified vaginitis, genital herpes, and chlamydia infection (*n* = 1). Pap smear screening had been undertaken at least once in 20 women and was abnormal in five patients (25%). One patient (patient 4, Table 5) had a history of recurrent abnormal pap smears. Clinical and laboratory immunodeficiency features were variable in patients with gynecologic infections and/or abnormal Pap smear (Table 5). None of the patients had received human papillomavirus (HPV) vaccination. The only gynecologic cancer reported was cervical cancer in one patient (69.8 years), diagnosed at the age of 48 years and treated surgically.

TABLE 3 Current and previous use of contraception reported by 25 CHH women

	Ever used (*n*)	Currently using (*n*)
Condom	15/25	
Combined contraceptive pills	15/25	1
Combined contraceptive ring	1/25	
Progestin only pills	10/25	2
Levonorgestrel-releasing device	3/25	
Intrauterine device (copper)	1/25	
Sterilization	7/25	3 (4 postmenopausal)
Partner sterilization	1/25	1
Any contraception	19/25	7

TABLE 4 Gynecologic concerns reported by the 26 women with CHH

Concern	Women self-reported, *n*	% of all patients
Heavy menstrual flow	2	8
Menstrual cycle irregularities	3	12
Dysmenorrhea	15	58
Recurrent gynecologic infections	7	27
Difficulties using tampon	3	10
Difficulties using topical vaginal treatment	2	8
Difficulties in sexual intercourse	2	8
Pregnancy complications	2	8
Health of offspring	2	8
Sexual assault/abuse	1	4

Gynecologic surgery had been performed in 11 patients: sterilization (*n* = 7), caesarean section (*n* = 8), hysterectomy (*n* = 2) endometrial ablation (*n* = 2), salpingo-oophorectomy (*n* = 1), cystectomy (*n* = 1), and myomectomy (*n* = 1).

Nine women reported sexual health problems and concerns (Table 4). Many problems were related to short arms and short stature resulting difficulty using tampons or topical treatment for vaginal dryness, and anatomical and positional difficulties in sexual intercourse. Specific concerns were mainly related to potential pregnancy complications and health of offspring as well as sexual harassment and abuse. Six women reported that they had never attempted pregnancy because of worries about their own or their offspring´s health.

4 | DISCUSSION

We describe gynecologic health in a large (*n* = 26) cohort of adult women with CHH, highlighting a normal fertility period, absence of pregnancy complications, successful deliveries by caesarean section, relatively high prevalence of spontaneous miscarriages, and the need for prompt counseling to address personal concerns of these patients. In addition, recurrent gynecologic infections and abnormal Pap smears warrant special attention in this patient group.

Our study complements the very limited published data on pubertal, gynecologic and obstetric health in patients with skeletal dysplasias. Tyson et al. studied gynecologic and obstetric history in 13 females with achondroplasia and in 22 females with other skeletal dysplasias (Tyson, Barnes, McKusick, Scott, & Jones, 1970), noting that menarche was not delayed compared with the general population. In a small American series (*n* = 5), mean menarcheal age in women with CHH was slightly increased at 14.2 years (US mean 12.8 years) (Allanson & Hall, 1986). In a previous Finnish study consisting of 15 CHH women, mean age at menarche was 13 years, consistent with the results of our study (mean 12.7 years) and with data from the Finnish general population (mean 13.2 years) (Kantero & Widbolm, 1969; Mäkitie et al., 1992). Natural mean menopause age was slightly earlier (46.1 years) than in the general population in

TABLE 5 Variable clinical and laboratory manifestations of immunodeficiency in patients with cartilage-hair hypoplasia and recurrent gynecologic infections and/or abnormal pap smear

	P1	P2	P3	P4	P5	P6	P7	P8	P9
Gynecologic infections	Condyloma accuminata	Nonspecific vaginitis	Condyloma accuminata, genital herpes	Recurrent candidiasis, chlamydia infection	Condyloma accuminata	Recurrent candidiasis	Recurrent candidiasis	None	None
Pap smear	Abnormal	Normal	Normal	Abnormal	Abnormal	Not taken	Normal	Abnormal	Abnormal
Susceptibility to infections	None	BE	OM requiring surgery, BE	None	BE, recurrent pneumonia and sin requiring surgery	NA	None	BE, OM and sin requiring surgery	Sin
Malignancies	None	BCC	Lymphoma	None	None	NA	None	Cervical cancer	None
Plasma levels of immunoglobulins[a]	Normal	Normal	Normal	Normal	Low IgM	NA	Normal	Low IgM	Normal
Lymphocyte counts[b]	Low total lymphocytes, CD3+, CD4+, CD8+, and CD19+ counts	Normal	Low CD8+	Normal	Low CD19+ counts	NA	Low total lymphocytes	Low CD19+ counts	Low CD19+ counts
Lymphocyte proliferation responses[c]	NA	NA	Abnormal	Abnormal	NA	NA	Normal	NA	Abnormal
SAD[d]	NA	NA	None	None	None	NA	Yes	NA	NA

BCC = basal cell carcinoma; BE = bronchiectasis; Ig = immunoglobulin; NA = data not available; OM = recurrent otitis media; SAD = specific antibody deficiency; S_{sin} = recurrent rhinosinusitis.

[a] Local laboratory reference values were applied, measured as described previously in Kostjukovits, Klemetti, et al., 2017.

[b] Local laboratory reference values were applied, measured by flow cytometry as described previously in Kostjukovits, Klemetti, et al., 2017.

[c] Data were obtained from hospital records, measurement performed by various methods.

[d] SAD was defined as inadequate antibody response to Pneumovax®: a fourfold rise in antibody titers and postimmunization antibody levels ≥0.35 μg/mL to <70% of serotypes, measured as described previously in Kostjukovits, Klemetti, et al., 2017.

Europe and North America (50–51 years), however, our sample size was small (Nelson, 2008).

Data on fertility and pregnancy outcomes in women with CHH is very limited (Thavarajah & Berndl, 2017). In a Finnish series of women with CHH, six females were reported to be married to unaffected males. Two of these couples had two children and two had one child. All the children had been delivered by caesarean section and were healthy (Mäkitie, 1992). Another survey of obstetrical and gynecological outcomes in women with chondrodystrophies in 1986 included three women with CHH; however, details of their pregnancy outcome were not reported (Allanson & Hall, 1986). In our series, 38% of women reported pregnancy and 31% (8/26) had given birth. A total of 19 children were born to eight women.

All reported births in CHH patients in our cohort were via caesarean section delivery. Because repeated caesarean sections increase the risk for fetal and maternal complications and preterm birth, as well as problems with anesthesia and increased surgical risks, pregnancy follow-up and deliveries in women with CHH should be centralized and managed by a multidisciplinary team (DeRenzo, Vallejo, & Ramanathan, 2005; Thavarajah & Berndl, 2017). In this study, some women with CHH reported avoiding pregnancy because of fear of pregnancy complications or fear of delivering an affected child, highlighting the importance of appropriate, systematic obstetric, and genetic counseling.

An analysis of health-related quality of life found significantly more problems in patients with chondrodysplasias than in healthy controls, amongst them lower sexual activity (Apajasalo et al., 1998). The wide variety of contraception methods used by women with CHH may reflect difficulties finding a suitable method and lack of appropriate counseling. Short stature may have been unnecessarily considered a contraindication for intrauterine devices in some women with CHH. The levonorgestrel-releasing intrauterine device is an effective contraceptive method that also treats heavy menstrual flow and dysmenorrhea, and is widely used in Finland (Lindh et al., 2017). It may be a good option for women with CHH, many of whom (60%) reported dysmenorrhea. Additionally, because of the well-known risk for anemia in CHH, contraception methods decreasing menstrual flow may be beneficial.

A relatively high proportion of abnormal Pap smears and condylomata as well as one patient with cervical cancer in our series may indicate a vulnerability to HPV infection in patients with CHH. As especially prolonged HPV infections caused by high-risk HPV types predispose to cervical cancer, careful and systematic follow-up of abnormal Pap smears is of the utmost importance in immunodeficient CHH patients (Serrano, Brotons, Bosch, & Brun, 2017). Although condylomata are caused by nononcogenic subtypes of HPV, they may cause subjective symptoms and distress and are often recurrent and difficult to treat, particularly in immunocompromised patients. HPV vaccination should be strongly considered in subjects with CHH, although there is no data on its efficacy in this group of patients.

In summary, based on our cohort of 26 adult females with CHH we suggest that gynecologic and obstetric follow up of patients with CHH should be systematic and centralized. Psychosexual counseling, as well as genetic counseling should be an integral part of their management. More detailed studies of fertility and pregnancy outcomes in patients with CHH and in other skeletal dysplasias are needed.

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CONFLICT OF INTEREST

There are no potential conflict of interest concerning this manuscript by any of authors.

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