A survey of ovarian reserve and quality of life in female survivors of pediatric cancer

Sofia Nilsson\textsuperscript{1} | Marianne Jarfelt\textsuperscript{2} | Stina Järvholm\textsuperscript{3} | Linda Kluge\textsuperscript{3} | Ann Thurin-Kjellberg\textsuperscript{3}

\textsuperscript{1}Department of Obstetrics & Gynecology, Varberg Hospital, Varberg, Sweden
\textsuperscript{2}Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, Sahlgrenska University Hospital, Gothenburg, Sweden
\textsuperscript{3}Department of Obstetrics and Gynecology, Institute of Clinical Sciences, Sahlgrenska Academy, Sahlgrenska University Hospital, Gothenburg, Sweden

Correspondence
Sofia Nilsson, Department of Obstetrics & Gynecology, Varberg Hospital, Träslösvägen 68, 432 37 Varberg, Sweden.
Email: sofia.nilsson@regionhalland.se

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Abstract

Introduction: Childhood cancer is rare; the incidence in Sweden is approximately 16 new cases/100,000 children each year. Reduced reproductive function and fertility are well-known side effects of cancer treatment. Anti-Müllerian hormone (AMH) has been shown to correlate well with antral follicle count in healthy women but is currently not recommended as the primary surveillance modality for evaluation of premature ovarian insufficiency in this patient group. Psychological wellbeing related to fertility could affect quality of life and should be included in long-term follow-up. The aim of the study is to present the baseline data from inclusion for a prospective follow-up study of fertility surveillance where both medical and psychological aspects of fertility in female childhood cancer survivors are considered.

Material and methods: These are the first results from this longitudinal follow-up cohort study. Female adolescent and young adult survivors of pediatric cancer in Western Sweden were included from January 2016 to December 2018, a total of 54 participants. Median age at inclusion was 21 (15–29) years and median age at cancer diagnosis was 10 (1–17) years. AMH levels, antral follicle count, and data on fertility were recorded at inclusion and will be prospectively followed up. The study includes questionnaires and interviews concerning quality of life. This study is planned to continue until the participants reach the age of 40 years.

Results: Eighteen of 54 (33%) participants had AMH levels below 1.0 µg/L and were considered to have high or very high risk of infertility. Median AMH level was 2.50 µg/L. Six women had immediate need of oocyte cryopreservation. Psychological assessment showed that more than one-third of participants (n = 20) had elevated anxiety scores.

Conclusions: One-third of female survivors of pediatric cancer in the study had high risk of low ovarian reserve, measured by a combination of AMH and antral follicle count, and many had signs of anxiety. The longitudinal study could contribute to better

Abbreviations: AFC, antral follicle count; AMH, anti-Müllerian hormone; CCS, childhood cancer survivor; eCRF, electronic case report form; FSH, follicle-stimulating hormone; HADS, Hospital Anxiety and Depression Scale; POI, premature ovarian insufficiency; SCT, stem cell transplantation; SF-36, Short Form-36; SOC, Sense of Coherence.
1 | INTRODUCTION

Childhood cancer is rare; the incidence in Sweden is approximately 16 new cases/100 000 children below 15 years of age each year. In the west of Sweden, this results in a yearly incidence of 45–50 girls with cancer below the age of 18 years. Leukemia and central nervous system tumors account for 50% of the diagnoses. Cancer treatment can be gonadotoxic but this varies according to the chemotherapeutic agent and the type, dose and field of radiotherapy. Reduced fertility and premature ovarian insufficiency (POI) are well known side effects of cancer treatment but there is not enough knowledge of how individual differences may affect fertility. The main mechanism responsible for ovarian gonadotoxicity is related to DNA damage of primordial follicle oocytes, leading to chemotherapy-induced apoptosis.

Anti-Müllerian hormone (AMH), a marker of ovarian reserve, is detectable at birth, increases during childhood, and peaks at the age of 25. Thereafter, AMH levels decline gradually until menopause, when the hormone is undetectable. The biomarker has primarily been used to predict response to in vitro fertilization therapy and correlates well with antral follicle count (AFC). Measuring AMH has been suggested as a possible way to prospectively monitor ovarian reserve in female CCS. Already in 2007, Van Beek et al. used AMH as a marker of gonadal function in women who had been treated with chemotherapy for Hodgkin's lymphoma. They showed AMH to be a more sensitive predictor than follicle-stimulating hormone (FSH) and inhibin B for ovarian function, and suggested AMH be used during follow-up of CCS to predict development of ovarian failure. A study conducted in 2014 showed that one-third of CCS reported normal menstrual pattern, but had low AMH levels, suggesting some degree of POI and demonstrating the limitations of self-reported menstrual history as a measure of evaluating ovarian reserve. Fertility surveillance recommendations vary among existing long-term follow-up programs for female CCS and AMH is currently not recommended as the primary surveillance modality for evaluation of POI. This hinders implementation of generalized screening and monitoring practices.

Fertility among female CCS is found to be an important benchmark for a feeling of normalcy. An important aspect of quality of life, apart from fertility per se, is also general psychological well-being. Previous studies have shown divergent results in terms of anxiety and depression in this group of patients. An American study from 2013 demonstrated increased anxiety symptoms over time in CCS. This could indicate that other aspects influencing quality of life are also affected. A recent Swedish study found that young female cancer survivors were less satisfied with their sexual function compared to a control cohort. It has also been reported that young CCS consider future fertility and ability to have children as a quality of life priority. In a previous study, we found that CCS at the end of their fertile period had experienced a lack of information on their fertility during their adult life.

The method of cryopreservation of oocytes through vitrification was developed in the first decade of the millennium. The oocytes can later, when the woman desires pregnancy, be subjected to in vitro fertilization and embryo transfer. Clinical pregnancy rates per oocyte range from 4% to 12%, and from 36% to 61% per subsequent embryo transfer.

Recently, this technique is considered to be feasible for young adolescents who may just enter the pubertal stage or even in specific situations in the prepubertal stage. Another alternative is ovarian tissue cryopreservation. This can be performed directly, using laparoscopic surgery and without delaying cancer treatment, provided the patient is well enough. However, research has raised concerns about reintroducing malignant cells using the procedure. This approach is only used for patients that are in immediate need of cancer treatment, and when there is a very high risk of infertility. More than 130 cases of live births using this technique have been reported and it is the only option available for prepubertal girls. Recently, a case report of live births from patients who underwent ovarian tissue cryopreservation as prepubertal girls have been published, which is very encouraging.

Key message

Fertility surveillance among young female survivors of childhood cancer varies. One-third of the women had reduced ovarian reserve, measured by a combination of AMH and antral follicle count. Psychological well-being was also affected, indicating that psychological parameters should be included in long-term follow-up.

knowledge in the changes of AMH over time for this patient group. Psychological follow-up with questionnaires and interviews evaluating signs of depression and anxiety may serve as a model for future screening programs.

KEYWORDS

anti-Müllerian hormone, childhood cancer survivors, cryopreservation, fertility, longitudinal follow-up, quality of life

Cancer below the age of 18 years.

In previous studies, it was shown that gonadotoxic treatments lead to premature menopause in 8%-13% of females. However, young female childhood cancer survivors (CCS) at risk of impaired ovarian function after pediatric cancer treatment have so far rarely been offered fertility cryopreservation.

This hinders implementation of generalized screening and monitoring practices.
The aim of our study is to present the baseline data from inclusion for a prospective follow-up study of fertility surveillance in female CCS where both medical and psychological aspects are considered. We hypothesize that by monitoring ovarian reserve and offering oocyte cryopreservation when AMH and AFC suggest low ovarian reserve, in combination with monitoring of psychological well-being, this could not only increase chances of having children, but also increase quality of life for these women.

2 | MATERIAL AND METHODS

2.1 | Subjects

Fifty-four female survivors of pediatric cancer, treated with chemotherapy and/or radiotherapy, were included from in the study between January 2016 and December 2018. Median age at inclusion was 21 (15–29) years. The participants were identified through the Long-Term Follow-Up Clinic at the Oncology Department and the Pediatric Oncology Center at Sahlgrenska University Hospital in Gothenburg, Sweden. Written informed consent was obtained from all participants and, where participants were under 18 years of age, their guardian. The median age at cancer diagnosis was 10 (1–17) years and the median time since end of cancer treatment was 11 (1–23) years. Of 57 eligible subjects, only three declined participation; two did not want to be reminded of having had childhood cancer and one considered herself too ill to participate. A longitudinal prospective follow-up of the cohort is planned every 2 years in patients between 15 and 25 years of age and thereafter every 5 years, including measurement of AMH levels, data on fertility preservation, data on any pregnancies and assessment of quality of life parameters through questionnaires and interviews (see below). An extended interview is performed at 25–30 and 40 years of age. The follow-up is planned to continue until the women are approximately 40 years old (Table 1).

2.2 | Medical measures

An assessment of risk for gonadotoxicity for each participant was made according to the Swedish National Guidelines for long-term follow-up (Table 2). All women were examined at the Reproductive Medicine Center at Sahlgrenska University Hospital, Gothenburg, Sweden. Data collected included gynecological history on pubertal development, menarche, menstrual flow pattern, use of contraceptives or estrogen replacement therapy, and any previous pregnancies. Data was also collected on weight and height and any fertility cryopreservation performed before cancer treatment. Blood samples were collected for hormonal analysis and were also frozen for future research. Analysis of AMH levels (µg/L) was performed in all participants. In appropriate cases, the women were also examined with transvaginal sonography to assess AFC. At inclusion, FSH, luteinizing hormone, and estradiol were also analyzed to identify the women who were likely to benefit from immediate fertility cryopreservation.

It is a clinical experience from IVF that in women having high FSH values (>16 IU/L) and when AMH and AFC (if measured) are low, success with FSH-stimulation is not probable. However, regarding women receiving estrogen supplementation due to previously known POI, we performed no further hormonal analyses except AMH, so as not to discontinue their medication. When analyzing AMH levels, we used previously suggested cut-off values of <1.0 µg/L to indicate reduced ovarian reserve, and values <0.025 µg/L to predict impending ovarian insufficiency.38,39 Fertility-preserving treatment was offered in cases where the AFC or AMH indicated low ovarian reserve, but this was individually assessed and the patient’s history was also taken into account. Strict objective criteria for oocyte cryopreservation were not possible for this young cohort of CCS. The methodological approach was that the women with AMH >1 µg/L indicated good ovarian reserve and would not need oocyte cryopreservation. A level <0.025 µg/L would predict infertility and hence it would be too late for cryopreservation. The women in the intermediate group, between 0.025 and 1.0 µg/L, are the cases likely to benefit from cryopreservation, but even so there was an individual and explorative approach as to who would go through the process. The women with induced puberty are by definition in POI and not candidates for cryopreservation but will anyway be followed up with AMH levels and psychologically in this study. Women with intermediate AMH levels but high FSH, would also not be candidates for cryopreservation, as this is unlikely to succeed. An electronic case report form (eCRF) regarding demographic data, type of cancer, treatment protocol, cumulative doses of chemotherapy, radiation field and dose, and gynecological history was filled in retrospectively at inclusion. This eCRF will store the participants’ data anonymized, but coded, in the Sahlgrenska University Hospital computer system without any participants’ names or identification numbers. The same eCRF will be used prospectively after inclusion for the future visits planned.

2.3 | Psychological measures

At inclusion, the participants answered several questionnaires including the Short Form-36 (SF-36), Hospital Anxiety and Depression Scale (HADS), and Sense of Coherence Scale (SOC-13) regarding mental health and quality of life parameters. The SF-36 questionnaire is a widely used tool to measure quality of life in medical research.40 The questionnaire consists of eight dimensions that encompass both physical and mental wellbeing. The normative total score for the general Swedish population is 79.6.40 Data from the present study was compared with data from a Swedish study from 2005 collecting norm data for SF-36 (n = 583). In all comparisons of the SF-36, data for a group of women 20–23 years of age was used (n = 83).41

Mood was analyzed using HADS, a validated self-report psychological instrument evaluating risk of depression and anxiety.42 HADS includes 14 questions with a score of up to 3 points per question, consisting of two seven-item joined subscales (HADS Depression and HADS Anxiety). The cut-off values, determined as borderline and in need of clinical assessment, are 8 out of 21 for
### Table 1: Flow chart showing the entire study protocol

| Study Component | 15–17 years of age \(^a\) | Reaching maturity at 18 years of age | Visit at 20 years, and every 2 years until 25 years | Visit at 25 years | Visit at 30 years | Visit at 35 years | Visit at approximately 40 years of age |
|-----------------|--------------------------|--------------------------------------|-----------------------------------------------|------------------|------------------|------------------|-------------------------------|
| Information regarding study participation and written consent, patients <18 years of age | x | | | | | | |
| Information regarding study participation and written consent (from the guardian because patient <18 years of age) | x | | | | | | |
| Information regarding study participation and written consent, patients ≥18 years of age | x | | | | | | |
| Filling in eCRF | x | x | x | x | x | x |
| AMH (FSH, LH, E2) | x | x | x | x | x | x | x |
| Frozen blood samples x 2 | x | x | x | x | x | x | x |
| Acute fertility preservation (where needed) | x | x | x | x | | | |
| Questionnaires x 3 | x | x | x | x | x | x |
| Short interview | x | x | x | x | x | x | x |
| Extended interview\(^b\) | x | | | | | | |
| Vaginal ultrasound + AFC, where possible | x | | | | | | |

AFC, antral follicle count; AMH, anti-Müllerian hormone; E2, estradiol; eCRF, electronic case report form; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

\(^a\) Patients were included up to 29 years of age. Some were therefore older than 18 at inclusion.

\(^b\) The patient included at 26–29 years old had an extended interview at inclusion.
each scale and there is a high likelihood of either condition being present if the score is 11 or more out of 21.43 The HADS score of the present study group was compared with that of a group of women \((n = 111)\), aged 30–39, participating in the Swedish evaluation of the scale in 1995.44

The SOC-13 comprises 13 items that measure comprehensibility, manageability and meaningfulness. The scale relates both to how individuals cope with illness concerning psychological symptoms and to physical health outcomes and recovery in, for example, cancer and rheumatism.45,46 The sense of coherence (SOC) items are measured on a semantic scale from 1 to 7, with a total score of 13–91 points. Scores up to 60 indicate low SOC, scores of 61–75 indicate moderate SOC, and scores over 76 suggest high SOC. For comparison of SOC-13 scores, a subgroup of women \((n = 47)\) aged 30 years, from a study of a random Swedish sample, was used \((n = 589)\).47

### 2.4 Statistical analyses

The study group characteristics at baseline are described using descriptive statistics with mean, standard deviation (SD), median and range for continuous variables, and number and percentage \((n, \%)\) for categorical and dichotomous variables. Descriptive statistics are used to analyze the questionnaire answers, and results are presented and compared with other study samples using the interactive two-sample t-test (https://www.evanmiller.org/ab-testing/t-test.html). A \(p\) value of <0.05 is considered statistically significant. All statistical analyses will be performed using IBM Statistical Package for the Social Sciences (SPSS), version 25 (IBM). Between-group comparisons of change from baseline to future follow-up visits will be analyzed using Fisher’s exact test for dichotomous variables and the Mann–Whitney U test for continuous variables.

### 2.5 Ethical approval

Ethical approval was granted by the Regional Ethics Board, University of Gothenburg, Sweden (Dnr: 349-15) on 14 September 2015. Handling data will follow the Swedish Data Protection Act (SFS 1998:204)/GDPR and a notification of the data register has been sent to the Swedish Data Protection Authority.

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### TABLE 2 Types of chemotherapy and radiation therapy with estimated risk of infertility due to gonadotoxic injury

| Low risk | Intermediate risk | High risk | Very high risk |
|----------|-------------------|-----------|----------------|
| Vincristine | Cisplatin | Cyclophosphamide >9 g/m² | RT >10 Gy to ovaries |
| Methotrexate | Carboplatin | Iosfamide >60 g/m² | Allogeneic HSCT |
| Actinomycin D | Cyclophosphamide <9 g/m² | Procarbazine | Autologous SCT |
| Bleomycin | Iosfamide <60 g/m² | BCNU | |
| Mercaptopurin | CCNU <360 mg/m² | CCNU >360 mg/m² | |
| Vinblastine | 5-FU | RT <10 Gy to ovaries | |
| 5-FU | 5-fluorouracil | BCNU, carmustine | |
| CCNU, lomustine | Gy, Gray | HSCT, hematopoietic stem-cell transplantation | |
| RT, radio therapy | SCT, stem-cell transplantation | |

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### TABLE 3 Patient characteristics at first visit; \(n = 54\)

| Characteristics | \(n = 54\) |
|-----------------|-------------|
| Median age, years (range) | 21 (15–29) |
| Median time since end of cancer treatment, years (range) | 11 (1-23) |
| Age at cancer diagnosis, years (range) | 10 (1-17) |
| BMI, \(n, \%\) | |
| \(<18.5 \text{ kg/m}^2\) | 12 (22) |
| 18.5–24.9 \text{ kg/m}^2 | 33 (61) |
| 25–29.9 \text{ kg/m}^2 | 6 (11) |
| \(\geq 30 \text{ kg/m}^2\) | 3 (6) |
| Risk of infertility, \(n, \%\) | |
| Low | 11 (20) |
| Medium | 25 (46) |
| High | 7 (13) |
| Very high | 11 (20) |
| SCT, \(n, \%\) | 11 (20) |
| Menarche, \(n, \%\) | |
| Spontaneous | 48 (89) |
| Induced | 5 (9) |
| Menstrual pattern, \(n, \%\) | |
| No menarche yet | 1 (2) |
| Regular | 21 (39) |
| Irregular | 7 (13) |
| Oral hormonal contraceptive/MHT | 25 (46) |
| Prior pregnancies, \(n, \%\) | |
| Yes | 3 (6) |
| No | 51 (94) |
| Eligible for fertility-preserving treatment at first visit, \(n, \%\) | |
| Yes | 6 (11) |
| No \(^a\) | 48 (89) |

**BMI**, body mass index; MHT, menopause hormone therapy; SCT, stem cell transplant.

\(^a\) One patient in this group had previous fertility-preserving intervention.
3 | RESULTS

3.1 | Characteristics

In our cohort, acute lymphatic leukemia and bone or soft tissue tumors were the most common types of cancer having affected almost half of the women, followed by Hodgkin’s lymphoma and central nervous system tumors. Baseline characteristics are summarized in Table 3. Eleven women were considered to have low risk of infertility (20%), 25 women to have medium risk (46%), and 18 to have high or very high risk of infertility (33%). One-fifth \((n = 11/54)\) of the women had undergone stem cell transplantation (SCT). The majority of the cohort (48/54) had had spontaneous menarche, five of them had induced menarche and one person had not yet, at the age of 16, had her first menstruation. Four women of the five with induced menarche had been treated with SCT. Nearly half of the women were taking oral hormonal contraceptive pills or estrogen replacement therapy at the time of the first visit. Three participants had been pregnant previous to inclusion in the study, but no live births were reported.

3.2 | Anti-Müllerian hormone values

The AMH values of the cohort at inclusion are presented in Figure 1. The mean AMH level for the cohort was 3.11 \((\text{range 0.02–12.9})\) \(\mu\text{g/L}\), with a SD of 3.17. The median AMH level was 2.50 \(\mu\text{g/L}\). Using the cut-off of 1.0 \(\mu\text{g/L}\), 18 women (33.3%) were considered to have reduced fertility. Of the 11 women that had undergone SCT, all had AMH levels below 0.5 \(\mu\text{g/L}\) and four below 0.025 \(\mu\text{g/L}\). These four had needed puberty induction.

3.3 | Fertility cryopreservation

Six women were offered fertility-preserving treatment at the first visit; the baselines are shown in Table 4. A graph of each woman’s AMH levels and total number of vitrified oocytes is presented in Figure 2.

3.4 | Quality of life

The mean and median scores on the different subscales regarding quality of life (SF-36) are shown in Table 5. The women in our study scored similarly to a comparison group of women on General health, Role physical, Vitality, Social functioning and Role emotional.\(^{41}\) For the subscales Mental health and Bodily pain, the study groups’ scores indicate better quality of life compared with the norm group \((p < 0.05)\). Regarding Physical function, women surviving childhood cancer reported significantly lower function than did the comparison group \((p < 0.05)\).\(^{41}\)

Comparing the women in the study group with a comparison group of Swedish women when analyzing mood using HADS, the participants reported significantly more symptoms of anxiety \((p < 0.05)\); however, no significant difference regarding levels of depression was found.\(^{44}\) Our analysis of the present results showed that 20 of 54 had elevated anxiety scores of above eight, indicating need for clinical assessment. We saw no significant association between women with low AMH levels and elevated anxiety scores. When looking at the depression subscale, five participants scored above 8, indicating a need for clinical assessment.

Regarding SOC, the women in the present study reported a significantly lower level \((p < 0.05)\) than a comparison group of young women.\(^{47}\) In the present study, four women (7%) had a high, 29 (53%) a moderate, and 21 women (40%) a low SOC.

4 | DISCUSSION

This is a presentation of the first data from a long-term follow-up study of young women who survived childhood cancer where we measured AMH levels and AFC as well as performed psychological

![AMH values](chart.png)
assessment. In this cohort, one-third of the women were considered to have a high or a very high risk of infertility; this group included all women who had been treated with SCT. Six of the 54 women included were in need of immediate fertility preservation.

Elevated anxiety scores were noted in 37% of the participants. The reported anxiety in this group was significantly increased compared with other young women. We have not been able to see a connection between reduced fertility and increased self-reported anxiety at this stage. Regarding symptoms of depression, 91% of the cohort did not report scores above threshold for clinical assessment, which is comparable to a control group of young Swedish women.

The increased reported mental strain can, of course, be related to the women’s previous medical history, but could also be associated with present stressors, such as concern about fertility or post-traumatic stress, which has been reported elsewhere.

The continued longitudinal follow-up study is important because of its prospective longitudinal design, making it possible to investigate whether systematic surveillance of ovarian reserve in female CCS can predict when fertility starts to decline and to identify who should be offered fertility cryopreservation. The need for personalized health assessment has previously been found to be important, since only a minority of women (17%) in the female CCS group would bring up the question of fertility themselves. By prospectively collecting data on life quality parameters, through questionnaires and interviews, we will be able to conclude whether the structured follow-up and fertility preservation interventions, when needed, affect wellbeing and quality of life, and we will be able to offer assistance to women in need of psychological therapy.

The reason for surveillance of ovarian reserve using AMH is that AMH is stable throughout the menstrual cycle; also, it is more sensitive than FSH when studying follicle reserve. A high level of FSH is what has traditionally been understood to indicate premature ovarian failure, due to negative feedback in the hypothalamic-pituitary-ovarian axis. However, once the FSH level is high, it is too late to

### Table 4

Baseline data of Anti-Müllerian Hormone level and number of oocytes vitrified in patients offered fertility preservation treatment at inclusion

| Patient | AMH value (µg/L) | Oocytes cycle 1 | Oocytes cycle 2 | Oocytes cycle 3 | Total FSH dose IU (first cycle) |
|---------|------------------|----------------|----------------|----------------|-------------------------------|
| 1       | 0.56             | 4              | 5              | 9              | 4925                          |
| 2       | 1.90             | 4              | 10             | –              | 3300                          |
| 3       | 0.74             | 4              | 5              | 3              | 4975                          |
| 4       | 0.66             | 6              | –              | –              | 3975                          |
| 5       | 1.15             | 10             | –              | –              | 2250                          |
| 6       | 0.28             | –              | –              | –              | 4950                          |

AFC, antral follicle count; AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; POI, premature ovarian insufficiency.

1 Low AFC and suspected POI despite normal AMH.

2 Ceased stimulation as no response.

**TABLE 4** Baseline anti-Müllerian hormone (AMH) values and number of vitrified oocytes in each patient (1–6)
TABLE 5 Participants’ quality of life (SF-36), mood, anxiety (HADS), depression (HADS) and sense of coherence (SOC-13) scores at inclusion

| Psychological domains with scales and subscales | Mean (SD) | Median (range) |
|-----------------------------------------------|-----------|----------------|
| Quality of life: SF-36                        |           |                |
| General health                               | 70.1 (22.5) | 75 (0–100) |
| Physical function                             | 91.6 (12.3) | 95 (45–100) |
| Role physical                                 | 78.4 (33.2) | 100 (0–100) |
| Bodily pain                                   | 82.2 (23.0) | 90 (10–100) |
| Vitality                                      | 58.8 (21.4) | 65 (10–90) |
| Social functioning                             | 83.9 (21.3) | 100 (25–100) |
| Role emotional                                | 77.2 (34.8) | 100 (0–100) |
| Mental health                                 | 73.7 (15.4) | 76 (12–100) |

| Mood: HADS                                    |           |                |
| Anxiety                                       | 6.7 (3.7)  | 6 (0–19)       |
| Depression                                    | 2.7 (2.9)  | 2 (0–13)       |

Sense of coherence: SOC-13

| Total score | 62 (11.3) | 64 (31–79) |

HADS, hospital anxiety and depression scale; SD, standard deviation; SF-36, short form 36; SOC-13, sense of coherence-13 scale.

For continuous variables, mean values (SD) are presented.

aData missing for two participants.

bData missing for three participants.

cData missing for one participant.

perform fertility cryopreservation. Normal AMH levels are ca. 5 µg/L for women at 20 years of age; thereafter the levels steadily decrease and by 40 years of age, the levels are around 1 µg/L. Nearly half of the women in our study were taking oral contraceptive pills, which further underlines the need to analyze hormone levels that are not affected by estrogen supplement in order to predict POI, making AMH a good candidate. The participants in our study who had just had analysis of AMH did not have to discontinue their medication (hormonal contraceptive pills or estrogen replacement therapy).

The majority (67%) had AMH levels above 1.0 µg/L, which was reassuring, although one subject had low AFC despite a normal AMH of 1.90 µg/L. This indicates individual variance in our study group, in contrast to the results reported in a previous study by Nyström et al., which showed good coherence between AMH and AFC in CCS. Our data suggest that fertility assessment could benefit from including AFC as well as AMH.

Twenty-two percent of the women in our cohort were underweight, which is three times as many as expected when compared with the age- and sex-adjusted figures from a general Swedish population. Whether this is due to medical reasons, anxiety or other psychological illness, or just coincidence, has to be investigated further.

Nearly half of the women in the study (46%) were taking oral hormonal contraceptive or menopausal hormone therapy. Some previous studies have shown that oral hormonal therapy can suppress AMH levels, whereas others have not. The women with intermediate AMH level (0.025–1.0 µg/L) who were candidates for oocyte vitrification and needed further analysis of FSH level did have their medications discontinued. The remaining participants did not pause their medications, as the potential benefit of receiving an exact AMH value did not weigh up against the negative effects of the woman ceasing her hormonal substitution. It is, of course, a limitation in the study that this could interfere somewhat with the AMH value.

The longitudinal study is designed to follow this group of women over several years until the age of approximately 40 and an obvious limitation is, of course, whether this is a feasible time frame. A concern in this type of design is whether there will be a continuity of staff at the clinic and whether the participants will continue to participate long-term, especially if their lives change.

5 | CONCLUSION

Our study showed that in this cohort of young female survivors of childhood cancer, one-third had low ovarian reserve, as measured by a combination of AFC and AMH. The longitudinal study would contribute to better knowledge in the changes of AMH over time for this patient group and AMH could be a candidate as a primary surveillance modality of fertility. Psychological well-being was also affected and 37% had elevated anxiety scores, suggesting need for clinical assessment. This strengthens the hypothesis that psychological parameters need to be included in long-term follow-up and our method using questionnaires and interviews may serve as a model for future screening programs.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

The study concept was designed by ATK, SJ and MJ. ATK and LK included the participants and transformed the data into the eCRF. SN prepared the first draft of the manuscript. All authors provided edits and comments and all authors approved submission.

ORCID

Sofia Nilsson https://orcid.org/0000-0002-7127-889X

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