

Oncofertility care evaluation of 599 children and adolescents with cancer and a high risk of treatment-induced gonadal damage: a national paediatric oncology cohort study

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ABSTRACT

STUDY QUESTION: What is the quality of our standard oncofertility care, with a focus on fertility counselling and preservation rates, in children and adolescents with cancer and a high risk of treatment-induced gonadal damage (HR^{gd}) at our national centralised paediatric oncology centre?

SUMMARY ANSWER: Standardised personalised oncofertility care was achieved in 66.1% of identified HR^{gd} children and adolescents with cancer, of whom 60.1% of patients underwent fertility preservation methods.

WHAT IS KNOWN ALREADY: Increasing survival rates among childhood cancer patients have heightened awareness of long-term treatment-related toxicities, including gonadal damage and subsequent risk of infertility. The American Society for Reproductive Medicine and the International Guideline Harmonization Group recommend that fertility preservation counselling should be offered to paediatric and adolescent cancer patients at high risk of gonadal damage, including consideration of gonadal tissue preservation when appropriate. However, evidence on the implementation of oncofertility care programmes in HR^{gd} paediatric and adolescent cancer patients remains limited.

STUDY DESIGN, SIZE, DURATION: This descriptive cohort study reports on standard oncofertility care in a national prospective cohort of HR^{gd} childhood cancer patients, between January 2020 and December 2023, in our national paediatric oncology centre.

PARTICIPANTS/MATERIALS, SETTING, METHODS: In all HR^{gd} childhood cancer patients, who were diagnosed or relapsed between January 2020 and December 2023 in the Princess Máxima Center, our standard oncofertility care strategy was evaluated. Prospective collection of demographics, tumours, treatment, and oncofertility care details, as well as retrospective collection and analysis of reasons why HR^{gd} patients and their families were not counselled or did not undergo fertility preservation, was performed.

MAIN RESULTS AND THE ROLE OF CHANCE: Between January 2020 and December 2023, 599 patients (age range 0–23 years; 345 males, 254 females) were triaged as HR^{gd} (459 children newly diagnosed and 140 relapsed patients), including 396 (66.1%) who were counselled with 238 of these (60.1%) undergoing fertility preservation. Reasons why HR^{gd} patients did not receive fertility counselling (n = 203/599, 34%) included their clinical status at diagnosis, young age of the patient, and anticipated poor prognosis. Uncertainties regarding future reproductive outcomes after autotransplantation of preserved tissue and concerns about potential risks of preservation procedures, were reasons for HR^{gd} patients (n = 158/396, 40%) to refrain from fertility preservation.

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LIMITATIONS, REASONS FOR CAUTION: Triage information of HR^{gd} patients who were diagnosed and/or relapsed during the establishment of oncofertility care in our centre may still be lacking.

WIDER IMPLICATIONS OF THE FINDINGS: Further improvement in oncofertility care is warranted by counselling all HR^{gd} patients and offering all of them gonadal tissue preservation through standardised documentation, whenever applicable. Future knowledge on reproductive and safety outcomes after cryopreservation and autotransplantation of gonadal tissue will further enhance fertility counselling.

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Introduction

Over the past decades, overall survival of childhood cancer has significantly increased to up to 80% in developed countries (Hudson *et al.*, 2014; Ward *et al.*, 2014; Ellison *et al.*, 2021; Botta *et al.*, 2022). The increasing number of childhood cancer survivors has raised awareness of direct and late toxicities of childhood cancer and its treatment (Oeffinger *et al.*, 2006). Preferably, these toxicities are anticipated and ideally prevented. A considerable subset of childhood cancer patients is at high risk for treatment-induced gonadal damage (further referred to as HR^{gd}), with potential subsequent infertility (Martinez and International Society for Fertility Preservation–ESHRE–ASRM Expert Working Group, 2017; Practice Committee of the American Society for Reproductive Medicine, 2019, 2026; Mulder *et al.*, 2021a,b; Meacham *et al.*, 2025; Mitchell *et al.*, 2025; Su *et al.*, 2025). Concern about the possible risk of infertility is among the main concerns of childhood cancer patients, survivors, and their families (Reh *et al.*, 2011; Anazodo *et al.*, 2019; Clasen *et al.*, 2023). Therefore, it is important that all children and adolescents with cancer are triaged regarding their risk of infertility and that adequate counselling on personal risk of treatment-induced gonadal damage and fertility preservation methods is offered at least to HR^{gd} patients, preferably before or early during treatment (Letourneau *et al.*, 2012; Deshpande *et al.*, 2015; Skaczkowski *et al.*, 2018; Newton *et al.*, 2021; Clasen *et al.*, 2023). Our previous report on the utilisation of a standardised oncofertility care plan for female patients with cancer in the starting phase of our national paediatric oncology centre showed that personalised oncofertility care is feasible (van der Perk *et al.*, 2021). To identify all HR^{gd} patients, according to international definitions and guidelines (Martinez and International Society for Fertility Preservation–ESHRE–ASRM Expert Working Group, 2017; Practice Committee of the American Society for Reproductive Medicine, 2019, 2026; Mulder *et al.*, 2021a,b; Meacham *et al.*, 2025; Mitchell *et al.*, 2025; Su *et al.*, 2025) and to again triage patients at the time of relapsed disease was identified as an important challenge for future practice. So far, reports on oncofertility programmes with respect to fertility preservation in national cohorts of HR^{gd} paediatric and adolescent cancer patients are scarce. Here, we aim to determine the quality of our standard oncofertility care, focusing on triage, fertility counselling, and the fertility preservation offered to HR^{gd} paediatric and adolescent

cancer patients in our national paediatric oncology centre over four consecutive years (2020–2023).

Materials and methods

Ethical approval

Ethical consent had been obtained from the METC Utrecht (Medical Ethical Committee Utrecht) for the PEARL and the PRINCE study. Description of data was approved through BioBank consent (Project number PMCLAB2023.0388).

Patients

All newly diagnosed and relapsed childhood cancer patients, independent of age, identified by triage as carrying a high risk of gonadal damage according to our oncofertility care plan (Supplementary Table S1), and treated at the Princess Máxima Center, a national paediatric oncology centre, between January 2020 and December 2023, were included in this study. Patients aged >18 years (Table 1) who received treatment according to a paediatric treatment protocol were also included to ensure comprehensive reporting and complete capture of fertility counselling and preservation within our centre. This subgroup consisted of patients treated for a relapse of childhood cancer, with a primary diagnosis before the age of 18 years ($n = 13$), patients with a cognitive impairment requiring continued paediatric oncology care ($n = 4$), or patients treated in our centre according to the ALLTogether protocol (Supplementary Table S1), which is exclusively provided at our paediatric cancer centre in a research context ($n = 10$).

Risk stratification tool

Based on international guidelines and consensus (Martinez and International Society for Fertility Preservation–ESHRE–ASRM Expert Working Group, 2017; Practice Committee of the American Society for Reproductive Medicine, 2019, 2026; Mulder *et al.*, 2021a,b; Meacham *et al.*, 2025; Mitchell *et al.*, 2025; Su *et al.*, 2025), patients were identified and triaged regarding their gonadal damage risk using our treatment-based risk stratification tool (Supplementary Table S1) by a dedicated oncofertility nurse practitioner (van der Perk *et al.*, 2021). The risk stratification tool takes into consideration expected

Table 1. Characteristics of HR^{gd} childhood cancer patients identified through standardised oncofertility triage in the Netherlands, January 2020 to December 2023.

	Total cohort (n = 599)		Male cohort (n = 345)		Female cohort (n = 254)	
	At new diagnosis (n = 459)	At relapse (n = 140)	At new diagnosis (n = 260)	At relapse (n = 85)	At new diagnosis (n = 199)	At relapse (n = 55)
Median age at diagnosis, years (range) ^a	8.0 (0.0–22.0)	–	10.0 (0.0–22.0)	–	6.0 (0.0–22.0)	–
Median age at relapse, years (range) ^a	–	11.0 (0.0–23.0)	–	12.5 (0.0–23.0)	–	10.0 (1.0–23.0)
Diagnosis						
Haemato-oncologic malignancies (%) ^b	126 (27)	74 (53)	86 (33)	46 (54)	40 (20)	28 (51)
Acute lymphoblastic leukaemia	43 (9)	47 (34)	36 (14)	31 (36)	7 (4)	16 (29)
Acute myeloid leukaemia	18 (4)	16 (11)	10 (4)	9 (11)	8 (4)	7 (13)
Other leukaemia's	10 (2)	4 (3)	7 (3)	2 (2)	3 (2)	2 (4)
Bone marrow failure/MDS	24 (5)	3 (2)	9 (3)	2 (2)	15 (8)	1 (2)
Hodgkin's lymphoma	10 (2)	2 (1)	9 (3)	1 (1)	1 (0.5)	1 (2)
Non-Hodgkin's lymphoma	21 (5)	2 (1)	15 (6)	1 (1)	6 (3)	1 (2)
Solid tumours (%) ^b	235 (51)	62 (44)	114 (44)	37 (44)	121 (61)	25 (45)
Neuroblastoma	80 (17)	21 (15)	43 (17)	13 (15)	37 (19)	8 (15)
Renal tumour	7 (2)	8 (6)	–	5 (6)	7 (4)	3 (5)
Osteosarcoma	9 (2)	8 (6)	4 (2)	3 (4)	5 (3)	5 (9)
Ewing sarcoma	47 (10)	10 (7)	21 (8)	6 (7)	26 (13)	4 (7)
Germ cell tumour	12 (3)	2 (1)	4 (2)	2 (2)	8 (4)	–
Soft tissue sarcoma	74 (16)	13 (9)	37 (14)	8 (9)	37 (19)	5 (9)
Carcinoma	5 (1)	–	4 (2)	–	1 (0.5)	–
Skin cancer	1 (0.2)	–	1 (0.4)	–	–	–
Central nervous system tumours (%) ^b	98 (21)	4 (3)	60 (23)	2 (2)	38 (19)	2 (4)
CNS tumour	98 (21)	4 (3)	60 (23)	2 (2)	38 (19)	2 (4)
Median age at fertility preservation, years (range) ^a	12.0 (0.0–22.0)	15.5 (1.0–21.0)	14.0 (0.0–22.0)	14.0 (14.0–20.0)	8.5 (1.0–18.0)	6.5 (1.0–21.0)

^a Twenty-seven patients were older than 18 years at inclusion. These patients were eligible because they had experienced a relapse after an initial diagnosis before 18 years of age (n = 13), had cognitive impairment requiring continued paediatric oncology care (n = 4), or were diagnosed with acute lymphoblastic leukaemia scheduled to be treated according to ALLTogether protocol in research context in our centre (n = 10).

^b Numbers in italic depict total number of patients per category, respectively.

CNS, central nervous system; HR^{gd}, high risk of gonadal damage; MDS, myelodysplastic syndrome; n, number of patients.

cyclophosphamide equivalent dose (CED) scores, myeloablative conditioning as part of haematopoietic stem cell transplantation (HSCT), as well as radiotherapy (pelvic, abdominal, or total body irradiation) (Martinez and International Society for Fertility Preservation–ESHRE–ASRM Expert Working Group, 2017; Practice Committee of the American Society for Reproductive Medicine, 2019, 2026; Mulder *et al.*, 2021a,b; Meacham *et al.*, 2025; Mitchell *et al.*, 2025; Su *et al.*, 2025). Age at treatment is not incorporated into the formal risk stratification algorithm, although gonadal susceptibility to treatment may vary across developmental stages. In 2021, the risk stratification tool was revised in accordance with consensus recommendations from the American Society for Reproductive Medicine (ASRM) and International Guideline Harmonization Group (IGHG) guidelines (Practice Committee of the American Society for Reproductive Medicine, 2019, 2026; Mulder *et al.*, 2021a,b). Following these updates, patients were stratified into high- and low-risk categories only. Specifically, lower cumulative CED thresholds for high-risk classification were adopted (≥ 4000 mg/m² for males and ≥ 6000 mg/m² for females). Hence, most patients previously classified as intermediate risk are now predominantly reclassified as high risk (van der Perk *et al.*, 2021).

Male patients with cancer

In the period from 2020 until and including 2023, all postpubertal male patients with cancer were actively counselled and encouraged to pursue semen cryopreservation (SP) as standard of care, regardless

of personal risk of gonadal damage (Mulder *et al.*, 2021a; Mitchell *et al.*, 2025). Additional fertility preservation methods in postpubertal HR^{gd} male patients included testicular sperm extraction (TESE), percutaneous epididymal sperm aspiration (PESA) and electrostimulation (ES), in case of an inability to produce sperm through masturbation (Mulder *et al.*, 2021a; Mitchell *et al.*, 2025). In addition, from October 2021, the PRINCE ('testicular bioPies in young boys diagnosed with cancer to cRyopreserve future fertility; towards a safe and feasible future autologous Cell therapy') study (METC research file NL73818.000.21 (METC-protocol number 0000002974)) started in our centre, which offered testicular biopsies (TB) to harvest gonadal stem cells as a potential gonadal tissue preservation method in pre- and peri-pubertal HR^{gd} male patients with a new diagnosis of childhood cancer in a research setting. In postpubertal males, TB and TESE were only performed if SP was not successful.

Female patients with cancer

For females with cancer, counselling by an oncofertility specialist (gynaecologist) was actively encouraged in patients with an anticipated high risk of gonadal damage after triage and referral by the oncofertility nurse practitioner. Fertility preservation options included ovarian tissue cryopreservation (OTC), oophoropexy in case of radiotherapy, and oocyte cryopreservation (OC) for postpubertal females aged ≥ 16 years. In some cases, the option of oocyte cryopreservation for donation by patients' mothers (age <38 years old) (Mulder *et al.*, 2021b) was discussed as part of fertility counselling.

These procedures were prospectively monitored as part of the PEARL ('PresErving ovArian function through cryopreservation and informing girls with cancer about infertility due to gonadotoxic treatment') study (METC research file NL72115.041.19 (METC-protocol number 19/783, Netherlands trial register number NL8192)).

Methods

Relevant anonymized data for the purpose of this descriptive study of a national prospective cohort of childhood cancer patients were extracted from medical records based on informed consent. To prevent missing patients, patients were identified by using the daily updated hospital registration dashboard of the Princess Máxima Center (van der Perk *et al.*, 2021). Prospective collection of baseline data included type of malignancy, age at diagnosis, cancer treatment regime, details on oncofertility care, as well as date of and age at fertility preservation if pursued. The reasons why patients had not been counselled on their high risk of gonadal damage, as well as why patients or families declined fertility preservation after counselling, were retrospectively retrieved from patients' electronic medical files and analysed.

According to our oncofertility care plan, all included patients were triaged for their gonadal damage risk at initial diagnosis, prior to the start of oncological treatment. Patients in whom triage was delayed until after the start of treatment included female patients diagnosed with leukaemia and all patients diagnosed with renal tumours. These particular patients were triaged 6–8 weeks after diagnosis upon establishment of complete remission and/or definitive treatment stratification based on postoperative risk and treatment. At the time of relapse, disease progression, and inadequate response to treatment or change of treatment, patients were triaged again prior to the start of relapse or intensification of cancer treatment. Data completion, cleaning, and analysis were performed in the summer of 2025.

For male patients newly diagnosed with cancer only, the analyses were stratified according to the period before and after the start of the PRINCE study (October 2021), where, in contrast to the female setting, TB were only offered to chemo-naïve males with a new cancer diagnosis according to protocol. For relapsed HR^{gd} male and female patients who were referred for fertility counselling and preservation, timing of oncofertility care was analysed and stratified into primary diagnosis and the time of relapse.

Statistical analysis

To account for uncertainty around key estimates, 95% CIs were calculated for key proportions, including counselling and fertility preservation uptake rates. In addition, Pearson's chi-square tests were used to compare rates of referral for counselling, counselling uptake, and fertility preservation uptake, with those reported in the previously published cohort from our centre (van der Perk *et al.*, 2021). A two-sided *P*-value of <0.05 was considered statistically significant.

Results

Children and adolescents with a new diagnosis of childhood cancer

Between 1 January 2020 and 31 December 2023, 459 patients with a new diagnosis of childhood cancer (260 males, 199 females) were triaged to be at high risk for treatment-induced gonadal damage

(Table 1; Fig. 1A and B; Supplementary Table S2). The median age at diagnosis of HR^{gd} patients was 8.0 years (range 0.0–22.0 years). HR^{gd} patients were diagnosed with haemato-oncologic malignancies (*n* = 126, 27%; *n* = 71/126 preceding HSCT), solid tumours (*n* = 235, 51%), and central nervous system (CNS) tumours (*n* = 98, 21%).

Children and adolescents with a relapse of childhood cancer

In that same period, oncofertility care was provided at the time of relapse of childhood cancer in an additional 140 patients (85 males, 55 females), who were triaged to be at high risk for treatment-induced gonadal damage (Table 1; Fig. 1A and B; Supplementary Table S2). The median age at the time of relapsed disease of HR^{gd} patients was 11.0 years (range 0.0–23.0 years). These patients were diagnosed with a relapse of haemato-oncologic malignancies (*n* = 74, 53%; *n* = 70/74 preceding HSCT), solid tumours (*n* = 62, 44%), and CNS tumours (*n* = 4, 3%).

Newly diagnosed male patients with cancer

The median age at diagnosis of HR^{gd} males (*n* = 260) was 10.0 years (range 0.0–22.0 years) (Table 1). They were diagnosed with haemato-oncologic malignancies (*n* = 86, 33%), solid tumours (*n* = 114, 44%), and CNS tumours (*n* = 60, 23%) (Table 1). Out of 260 male patients with a new malignancy, 112 (43%) were diagnosed prior to the start of the PRINCE study, and 148 (57%) were diagnosed after the start of the PRINCE study (Fig. 1A). Prior to the start of the PRINCE study, 73/112 males (65.2%; 95% CI 56.0–73.4%) were counselled, of whom 38 underwent fertility preservation (52.1%; 95% CI 40.8–63.1%, *n* = 31 SP, *n* = 3 ES, *n* = 2 TB pursued in another hospital, *n* = 1 SP combined with TB pursued in another hospital, *n* = 1 ES combined with PESA) (Fig. 1A; Supplementary Table S3). After the start of the PRINCE study in our centre, 86/148 males (58.1%; 95% CI 50.1–65.8%) received fertility counselling, of whom 56 underwent fertility preservation (65.1%; 95% CI 54.6–74.3%, *n* = 27 PRINCE biopsies, *n* = 24 SP, *n* = 3 PRINCE biopsies combined with TESE, *n* = 2 SP combined with TESE due to failure of sperm production through masturbation) (Fig. 1A; Supplementary Table S3).

Retrospective analyses showed that 101/260 male patients with a new diagnosis (39%) were not referred for fertility counselling (Table 2). Reasons for this were documented in 14 males (14%), and these included a poor clinical condition requiring a rapid start of oncological treatment after diagnosis, young age (including prepubertal patients prior to the start of the PRINCE study), anticipated poor prognosis, and the upfront palliative care treatment setting (Table 2). In the other 87/101 male patients, reasons as to why they were not counselled were not available from their medical records (Table 2).

In 65 out of 159 (41%) counselled HR^{gd} male patients, fertility preservation was not pursued (Table 3). Reasons for this were available in 45 patients (69%) and included young age (including prepubertal patients prior to the start of the PRINCE study), no time to delay oncological treatment, and prior initiation of gonadotoxic treatment, as these patients were not eligible for inclusion in the PRINCE study (Table 3).

Relapsed male patients with cancer

The median age at the time of relapse in HR^{gd} males (*n* = 85) was 12.5 years (range 0.0–23.0 years) (Table 1). Their relapse concerned

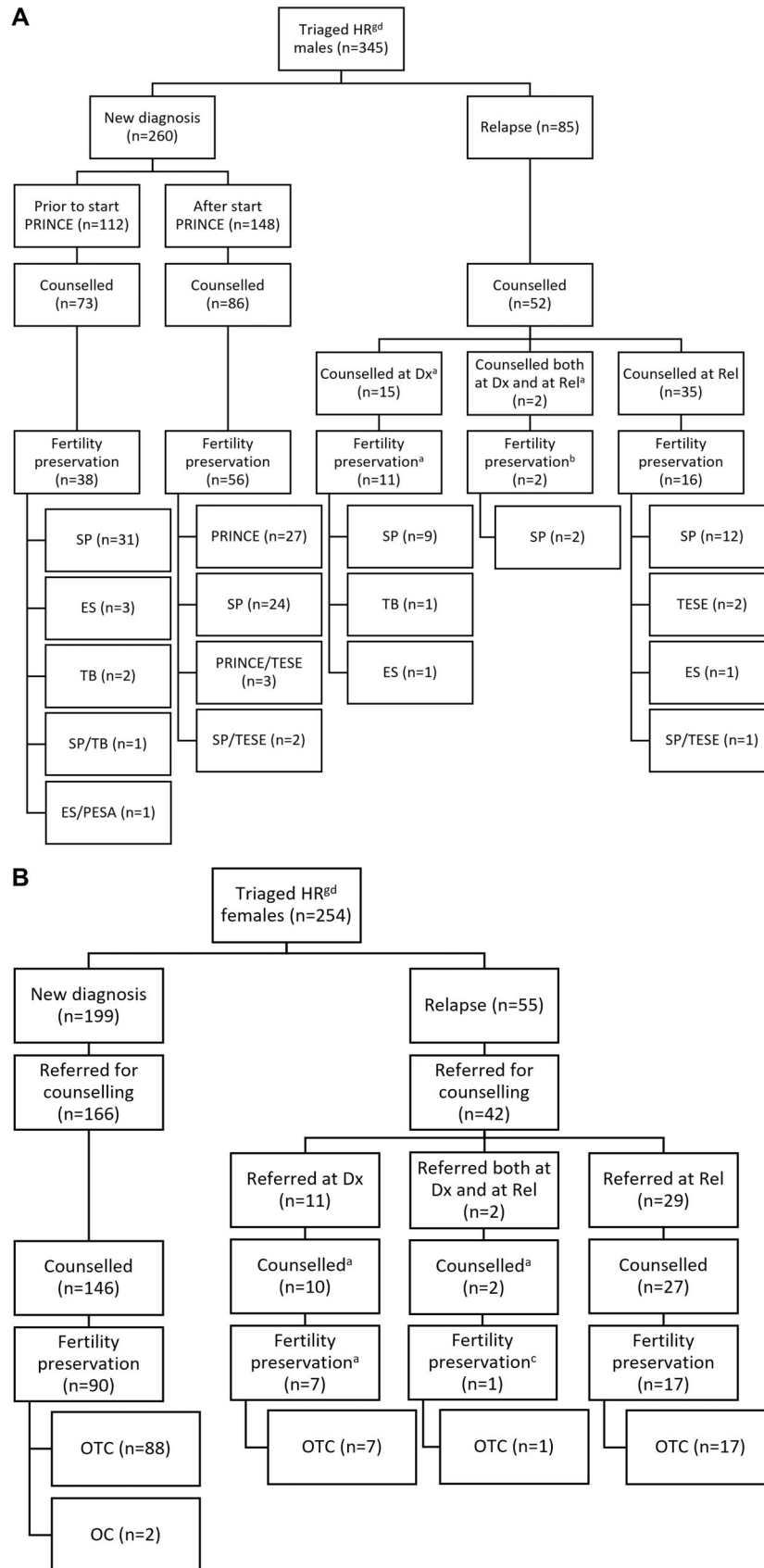


Figure 1. Standardised oncofertility care pathways in HR^{9d} paediatric and adolescent patients. (A) Flow chart of oncofertility care in HR^{9d} males (n = 345), stratified by newly diagnosed and relapsed disease, illustrating fertility counselling and fertility preservation pathways, with semen

Table 2. Reasons why healthcare providers did not provide fertility counselling to HR^{gd} patients after diagnosis.

	Male patients (n = 134)		Female patients (n = 69)	
	At new diagnosis (n = 101)	At relapse (n = 33)	At new diagnosis (n = 53)	At relapse (n = 16)
Young age ^a	5 (5)	1 (3)	2 (4)	–
Poor prognosis	3 (3)	1 (3)	2 (4)	–
Palliative care treatment setting	2 (2)	2 (6)	1 (2)	2 (13)
From a different country	2 (2)	1 (3)	3 (6)	–
Low gonadal damage risk ^b	–	–	2 (4)	–
Poor condition	1 (1)	–	1 (2)	–
Deceased early after diagnosis and/or relapse	–	–	4 (8)	–
Benign disease ^b	1 (1)	–	–	–
Pre-existing premature ovarian insufficiency	–	–	–	1 (6) ^c
Previous gonadotoxic treatment ^d	–	7 (21)	–	–
Not available	87 (86)	21 (64)	38 (72)	13 (81)

^a Prior to implementation of PRINCE study, pre- and peri-pubertal males were often not counselled by healthcare providers, due to the fact that fertility preservation options could not be offered. Females under the age of 1 year old at diagnosis could not be offered fertility preservation methods, as we do not perform elective ovarian tissue cryopreservation in females <1 year in our centre, for which reason they were not counselled.

^b Patients initially were triaged to be at high risk of gonadal damage, but due to a change of diagnosis and/or change of treatment plan after initial triage, patients were no longer considered to be at high risk and were therefore not counselled.

^c Patient was not diagnosed with a relapse, but with a secondary malignancy. She had pre-existing premature ovarian insufficiency as a result of her primary malignancy, for which reason she did not receive fertility counselling.

^d These prepubertal male patients were not counselled on their high risk of gonadal damage at relapse, since they could not be offered fertility preservation through testicular biopsies according to protocol.

HR^{gd}, high risk of gonadal damage; n, number of patients; PRINCE ('testicular bioPsies in young boys diagnosed with cancer to cRyopreserve future fertility; towards a safe and feasible future autologous CELL therapy' study), testicular biopsies in prepubertal boys in study context started in October 2021.

haemato-oncologic malignancies (n = 46, 54%), solid tumours (n = 37, 44%), and CNS tumours (n = 2, 2%) (Table 1). Out of 85 male patients with a relapse of childhood cancer, 52 (61.2%; 95% CI 50.6–71.0%) had received fertility counselling (n = 15 at primary diagnosis, n = 2 at primary diagnosis and again at relapse, n = 35 at relapse) (Fig. 1A). Of these, fertility preservation had been pursued by 29/52 males (55.8%, 95% CI 42.3–68.4%), including 11/15 males (73%, n = 9 SP, n = 1 TB pursued in another hospital, n = 1 ES) at primary diagnosis and 16/35 males (46%; 95% CI 30.5–61.8%, n = 12 SP, n = 2 TESE, n = 1 ES, n = 1 SP combined with TESE due to failure of sperm production through masturbation) at the time of relapsed disease (Fig. 1A, Supplementary Table S3). Of the two males counselled both at primary diagnosis and again at the time of relapse, one male pursued SP both at primary diagnosis and again at relapse because of azoospermia at his primary diagnosis and the other male at the time of relapsed disease only (Fig. 1A; Supplementary Table S3).

Reasons why HR^{gd} male patients and their families were not referred for fertility counselling at relapse (n = 33) were available in 12/33 males (36%) and included a young age, anticipated poor prognosis or palliative care treatment settings and prior initiation of gonadotoxic treatment (Table 2).

Reasons why fertility preservation was not pursued in relapsed HR^{gd} male patients (n = 23) were available in 12/23 patients (52%)

and included a young age, no time to delay, or a preference to prioritise oncological treatment, prior initiation of gonadotoxic treatment, and anticipated poor prognosis at the time of relapse (Table 3).

Newly diagnosed female patients with cancer

The median age at diagnosis in HR^{gd} females (n = 199) was 6.0 years (range 0.0–22.0 years) (Table 1). They were diagnosed with haemato-oncologic malignancies (n = 40, 20%), solid tumours (n = 121, 61%), and CNS tumours (n = 38, 19%) (Table 1). Of these, 166 (83.4%) were offered referral for fertility counselling by a gynaecologist, of whom 146 (73.4%; 95% CI 66.8–79.2%) subsequently accepted referral (Fig. 1B). Fertility preservation was pursued by 90/146 females (61.6%; 95% CI 53.5–69.0%, n = 88 OTC, n = 2 OC) (Fig. 1B; Supplementary Table S4).

Reasons why HR^{gd} female patients had not undergone fertility counselling at diagnosis (n = 53) were available in 15/53 patients (28%) and included a young age, anticipated poor prognosis, or upfront palliative care treatment setting (Table 2). Four HR^{gd} females who had not been referred for fertility counselling appeared to have died early after diagnosis.

Reasons why counselled HR^{gd} female patients (n = 56) and their families decided not to pursue fertility preservation were available for 49/56 patients (88%) (Table 3). Reasons included a preference to prioritise

Figure 1. Continued

cryopreservation as the most frequently performed fertility preservation procedure. (B) Flow chart of standardised oncofertility care in HR^{gd} females (n = 254), stratified by newly diagnosed and relapsed disease, illustrating referral, fertility counselling, and fertility preservation pathways, with ovarian tissue cryopreservation as the predominant fertility preservation procedure. ^aRelapse patients who had been counselled and had undergone fertility preservation at primary diagnosis, had been primarily diagnosed prior to 2020, and none of the relapse patients who preserved at primary diagnosis, were included in the left column under 'New diagnosis'. ^bOne male pursued fertility preservation at relapse; the other did so both at primary diagnosis and at relapse after azoospermia at primary diagnosis. ^cOne female pursued fertility preservation at relapse. Dx, primary diagnosis of childhood cancer; ES, electrostimulation; HR^{gd}, high risk of gonadal damage; n, number of patients; OC, oocyte harvest and cryopreservation; OTC, ovarian tissue cryopreservation; PESA, percutaneous epididymal sperm aspiration; PRINCE, testicular biopsies in prepubertal males in study context started in October 2021; Rel, relapse of childhood cancer; SP, semen cryopreservation; TB, testicular biopsies prior to start of PRINCE study in Amsterdam UMC before the start of the PRINCE study (Oct 2021); TESE, testicular sperm extraction.

Table 3. Reasons why HR^{gd} patients did not undergo or pursue fertility preservation after fertility counselling.^a

	Male patients (n = 88)				Female patients (n = 70)			
	At new diagnosis (n = 65)		At relapse (n = 23)		At new diagnosis (n = 56)		At relapse (n = 14)	
	Patient decision	Physician decision	Patient decision	Physician decision	Patient decision	Physician decision	Patient decision	Physician decision
Young age	11	3	6	1	3	2	–	–
No time to delay oncological treatment	–	8	–	1	–	1	–	–
Inability to produce semen	6	–	–	–	–	–	–	–
Previous or already started gonadotoxic treatment	–	4	–	1	–	3	–	–
Poor condition	1	1	–	–	2	7	–	–
Prioritisation oncological treatment ^b	2	–	2	–	24	–	1	–
No wish for treatment, including oncofertility care	2	–	–	–	–	–	–	–
Religious reasons	2	–	–	–	7	–	–	–
No (future) child wish	1	–	–	–	1	–	–	–
Low gonadal damage risk ^c	–	1	–	–	–	5	–	–
Poor prognosis	–	1	–	1	–	2	–	–
Concerns about risks of surgical preservation procedure	1	–	–	–	23	–	1	–
Uncertainty reproductive outcomes after utilisation of cryopreserved tissue	1	–	–	–	16	–	1	–
Concerns about the safety of auto-transplantation of cryopreserved tissue because of risk of MRD ^d	–	–	–	–	14	–	1	–
Potential effect of chemotherapeutic agents on the residual gonad	–	–	–	–	3	–	–	–
Tumour location and/or anatomy	–	–	–	–	–	3	–	–
Trust in future fertility or assisted reproductive options	–	–	–	–	3	–	–	–
Diagnosis-related ^e	–	–	–	–	–	1	–	–
Pre-existing premature ovarian insufficiency ^f	–	–	–	–	–	–	–	1
Return to homeland	–	–	–	–	1	–	1	–
Not available	20		11		7		11	

^a Some patients and families reported multiple reasons why they did not want to pursue fertility preservation, for which reason percentages cannot be reported.

^b Preference to focus on cancer treatment and avoid additional emotional burden or logistical complexity associated with fertility preservation during an already highly stressful period.

^c Patients initially were triaged to be at high risk of gonadal damage and received counselling, but due to a change of diagnosis and/or change of treatment plan after fertility counselling, patients were no longer considered to be at high risk and therefore did not pursue fertility preservation.

^d In this cohort, 15 female patients and their families declined fertility preservation because they were concerned with the safety of autotransplantation of cryopreserved ovarian tissue and the risk of minimal residual disease. Of these 15 females, 10 were diagnosed with a solid tumour (n = 5/45 (11%) neuroblastoma, n = 3/42 (7%) rhabdomyosarcoma, n = 2/30 (7%) Ewing sarcoma) and 5 with a haematological malignancy (n = 4/23 (17%) acute lymphoblastic leukaemia, n = 1/15 (7%) acute myeloid leukaemia).

^e Fanconi anaemia.

^f Patient was not diagnosed with a relapse, but with a secondary malignancy. She had pre-existing premature ovarian insufficiency as a result of her primary malignancy, for which reason she did not pursue fertility preservation.

HR^{gd}, high risk of gonadal damage; MRD, minimal residual disease; n, number of patients.

oncological treatment over fertility preservation, uncertainties regarding the future reproductive outcomes after autotransplantation of preserved tissue, concerns about the safety of autotransplantation of ovarian tissue considering the risk of minimal residual disease (MRD), concerns about possible risks associated with the surgical preservation procedure, and a poor clinical status at diagnosis (Table 3).

Relapsed female patients with cancer

The median age in HR^{gd} females (n = 55) at the time of relapse was 10.0 years (range 1.0–23.0 years) (Table 1). They were diagnosed with a relapse of haemato-oncologic malignancies (n = 28, 51%), solid tumours (n = 25, 45%), and CNS tumours (n = 2, 4%) (Table 1). Referral for counselling was offered to 42/55 (76.4%) females (n = 11 already at primary diagnosis, n = 2 at primary diagnosis and at relapse, n = 29 at relapse), after which 39 (70.9%; 95% CI 57.8–81.4%) were counselled (n = 10 at primary diagnosis, n = 2 at primary diagnosis and at

relapse, n = 27 at relapse). After counselling, 25 females (64.1%; 95% CI 48.4–77.3%, n = 25 OTC) underwent gonadal tissue preservation (n = 7 at primary diagnosis, n = 18 at relapse) (Fig. 1B; Supplementary Table S4). None of the relapsed HR^{gd} females who underwent fertility preservation at the time of primary diagnosis underwent fertility preservation again at the time of relapse.

The reasons why female patients (n = 16) and their families did not undergo fertility counselling at the time of relapse were available in only 3/16 patients (19%) and turned out to be the upfront palliative care treatment setting and pre-existing premature ovarian insufficiency as a result of her primary malignancy (Table 2).

Reasons why HR^{gd} female patients (n = 14) and their families decided to decline fertility preservation were available in 3 out of 14 patients (21%). A preference to prioritise oncological treatment over fertility preservation, concerns about possible risks associated with the surgical preservation procedure, uncertainties regarding future reproductive outcomes after autotransplantation of preserved tissue,

and concerns about the safety of autotransplantation of ovarian tissue considering the risk of MRD were among the reasons for females and their families to refrain from fertility preservation (Table 3).

Discussion

The objective of this study was to evaluate the quality of our oncofertility care, with a focus on triage, fertility counselling, and offered preservation in a national Dutch cohort of childhood cancer patients with an anticipated high risk of treatment-induced gonadal damage between 2020 and 2023. With this, we aim to identify opportunities to further enhance oncofertility care in this relevant subset of patients in the future. We identified 599 HR^{gd} patients (459 at diagnosis and 140 at relapse), based on our gonadal risk stratification tool (van der Perk *et al.*, 2021), of whom the majority ($n = 396/599$, 66.1%; 95% CI 62.2–69.8%) received fertility counselling, with fertility preservation being pursued by 238 of the 396 counselled HR^{gd} patients (60.1%; 95% CI 55.2–64.8%). Main reasons to decline the offer of fertility preservation were a young age, concerns about the potential risks associated with surgical preservation procedures, uncertainties regarding the future reproductive outcomes after autotransplantation of preserved gonadal tissue, and concerns about the safety of autotransplantation of ovarian tissue considering the risk of MRD.

Newly diagnosed male patients with cancer

Between January 2020 and December 2023, 61.2% (95% CI 55.2–66.9%) of all newly diagnosed HR^{gd} male patients had been counselled regarding their personal risk of treatment-induced gonadal damage and were offered the option of fertility preservation, which 59.1% (95% CI 51.3–66.5%) of counselled males decided to pursue (Fig. 1A; Supplementary Table S3). After the start of the PRINCE study, we observed an increase (52.1–65.1%) in fertility preservation as this could be offered to both pre- and peri-pubertal males (Figs 1A and 2A), and their ages were no longer the primary reason for parents to refrain from fertility preservation. However, a subset of parents declined testis tissue preservation because of uncertainties regarding future reproductive outcomes (e.g. pregnancy and live birth rates) following utilisation of testicular tissue, since the preservation of testicular tissue does not guarantee future pregnancy, as well as concerns about the risks associated with the surgical testis biopsy procedure. It has, however, been shown that performing TB in prepubertal males is a safe procedure, performed in many countries since 2020. Performing TB in this relevant subset of patients can be offered as standard of care as part of oncofertility care, when multidisciplinary expertise can be offered and if national and local regulations allow this (Mitchell *et al.*, 2025; Safrai *et al.*, 2025). Subsequent steps required for achieving future fertility are, however, still being optimised. Recent reports on maturation of pre- and peri-pubertal

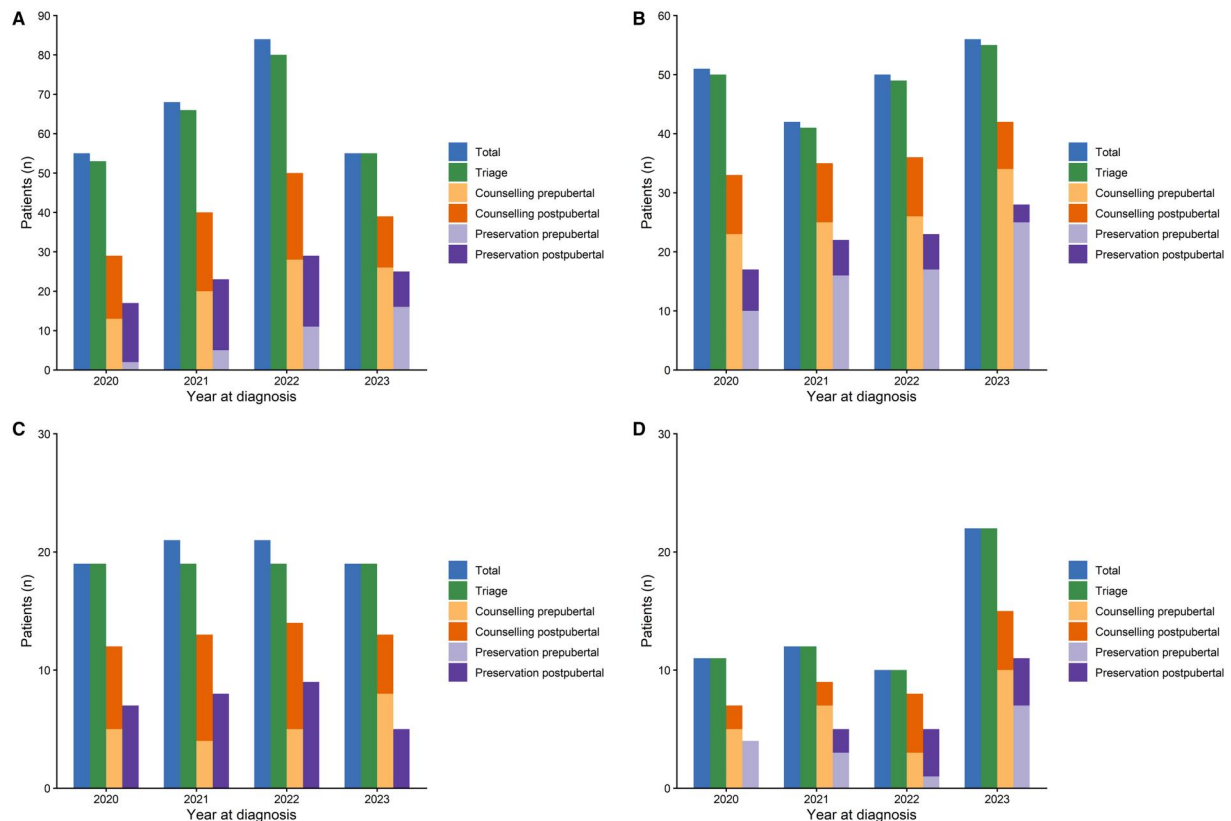


Figure 2. Annual implementation of standardised oncofertility care in HR^{gd} paediatric and adolescent patients (January 2020 to December 2023). (A) Annual number of newly diagnosed HR^{gd} male patients undergoing triage, fertility counselling and fertility preservation between 2020 and 2023. (B) Annual numbers of newly diagnosed HR^{gd} female patients undergoing triage, fertility counselling, and fertility preservation between 2020 and 2023. (C) Annual numbers of HR^{gd} male patients with relapsed cancer undergoing triage, fertility counselling, and fertility preservation between 2020 and 2023. (D) Annual numbers of HR^{gd} female patients with relapsed cancer undergoing triage, fertility counselling, and fertility preservation between 2020 and 2023. n, number of patients; HR^{gd}, high risk of gonadal damage.

testicular tissue, as well as reports on live births (>15) after maturation and autotransplantation of prepubertal testicular tissue in animal (including mice, rabbits, pigs and primates) models show promising results (Braye *et al.*, 2019; Fayomi *et al.*, 2019; Duffin *et al.*, 2024; Safrai *et al.*, 2025). With increasing research in this field of male fertility (Goossens *et al.*, 2026), more information will become available on the reproductive outcomes, with respect to pregnancy and live birth rates, after maturation and autotransplantation of pre- and peri-pubertal testicular tissue.

Newly diagnosed female patients with cancer

Between January 2020 and December 2023, 73.4% (95% CI 66.8–79.2%) of newly diagnosed HR^{gd} female patients had been counselled by a fertility specialist regarding their personal risk of gonadal damage, and 61.6% (95% CI 53.5–69.0%) of these females decided to pursue fertility preservation methods, with OTC the most prevalent procedure in this cohort (Fig. 1B; Supplementary Table S4). Concerns on the safety of surgical preservation procedures, as well as on reproductive outcomes after autotransplantation of ovarian tissue and the risks of autotransplantation considering the risk of MRD, were the main reasons for females and families to decline gonadal tissue preservation (n = 56, 38%) (Table 3). Our recent paper (Clasen *et al.*, 2026) on procedure-related complications in a subset of this cohort of 88 patients after laparoscopic oophorectomy, as well as additional literature (Clasen *et al.*, 2026) on the safety of laparoscopic OTC procedures show that OTC is a relatively safe and feasible procedure in paediatric and adolescent females with cancer, but that wound infections and bleeding do occur, even in controlled settings. As reports on the safety of laparoscopic oophorectomy in paediatric and adolescent cancer settings are limited, more studies in larger, preferably international, cohorts are needed to be able to evaluate the safety of OTC and improve fertility counselling. This information is included in the shared decision-making process of fertility counselling and preservation.

Reports of successful live births of healthy offspring (Corkum *et al.*, 2019; Gillipelli *et al.*, 2024; Emrich *et al.*, 2025) following autotransplantation of cryopreserved tissue in paediatric patients have increased interest in OTC for paediatric and adolescent females with cancer and reduced previous scepticism regarding this strategy. To date, 24 pregnancies resulting in 20 live births have been reported following 46 autotransplantations, including three live births after transplantation of ovarian tissue cryopreserved before puberty (at ages 9 and 13 years) in two females (Corkum *et al.*, 2019). In postpubertal subjects, more experience with autotransplantation, as part of standard of care, is available (Khattak *et al.*, 2022; Meacham *et al.*, 2025; Su *et al.*, 2025). Since literature on reproductive outcomes after autotransplantation of cryopreserved ovarian tissue in (prepubertal) children and adolescents is limited and the preservation of ovarian tissue does not guarantee future pregnancy, additional cohort studies are needed, particularly in young (prepubertal) females with cancer, to adequately address patients' and parents' concerns about the future benefits and reproductive outcomes of this procedure. Another reason to decline gonadal tissue preservation procedures was the concerns about the risks of autotransplantation considering the possibility of re-implanting tissue with MRD, thus causing a possible relapse of malignant disease (Dolmans *et al.*, 2010). A significant subset of patients with a high risk of gonadal damage is those diagnosed with a haemato-oncologic malignancy. Currently, there is no international consensus on whether it is safe to transplant ovarian tissue in

this subgroup of patients, nor in which patients ovarian tissue can safely be autotransplanted (Dolmans *et al.*, 2013; Kourta *et al.*, 2023). More research is needed on the safety of autotransplantation with regards to the possibility of MRD, to be able to address these concerns and risks during fertility counselling.

We previously described our first-year experience in the year 2019 at the start of our oncofertility care programme. Compared to the previous study (van der Perk *et al.*, 2021), we found that more HR^{gd} females were offered referral for counselling (83.4% vs 64.4%, Pearson $\chi^2 = 8.232$, $P = 0.004$) and counselled (73.4% vs 55.6%, Pearson $\chi^2 = 5.553$, $P = 0.018$) between 2020 and 2023 compared to the first year of oncofertility care (Fig. 2B). Fertility preservation rates were similar between the two cohorts (61.6% vs 64.0%, Pearson $\chi^2 = 0.050$, $P = 0.823$) (Fig. 2B). Compared to available literature on rates of fertility counselling and preservation in cancer patients (Table 4) (Ben-Aharon *et al.*, 2016; Kapadia *et al.*, 2020; Lehmann *et al.*, 2020; Gregoire-Briard *et al.*, 2022; Heritage *et al.*, 2022; Ligon *et al.*, 2023; Stukaite-Ruibiene *et al.*, 2023; Grimes *et al.*, 2024; Hartup *et al.*, 2024; Leavitt *et al.*, 2024; McElhinney *et al.*, 2024; Corona *et al.*, 2025), we report high rates of fertility counselling and similar rates of fertility preservation. However, none of the other studies reported findings on national cohorts nor stratified for newly diagnosed or relapsed patients.

Relapsed patients with childhood cancer

One of the lessons learned from our first evaluation of our oncofertility care setting was that we tended not to pay attention to a child's risk of gonadal damage at the time of relapse or when treatment is intensified (n = 3) (van der Perk *et al.*, 2021). Now, in the subsequent cohort, we found that patients are better identified and increasingly referred for counselling, counselled, and offered fertility preservation at the time of relapse or when treatment is intensified (Figs 1A and B and 2C and D). Hence, this indicates that more awareness has improved our oncofertility care for HR^{gd} patients over recent years, at diagnosis and again at relapse (Fig. 2C and D). An interesting observation is the increasing number of male patients receiving fertility counselling over time (Fig. 2A and C), while this was not accompanied by a proportional increase in fertility preservation procedures. This pattern was not explained by any identifiable systematic changes in counselling practices, referral pathways, or access to fertility preservation services within our dataset. It may reflect individual decision-making processes following counselling, including patient preference, timing constraints, or perceived urgency of oncological treatment, but these factors were not systematically captured in this study.

Future perspectives

Still, oncofertility care for children and adolescents with cancer can be further improved by timely triaging and ensuring fertility counselling and preservation for all HR^{gd} patients in accordance with guidelines by the ASRM and the IGHG (Letourneau *et al.*, 2012; Deshpande *et al.*, 2015; Skaczkowski *et al.*, 2018; Newton *et al.*, 2021; Clasen *et al.*, 2023). For a substantial proportion of patients, documented reasons why they did not receive fertility preservation counselling (Table 2) or declined fertility preservation methods (Table 3) were not available, mainly due to the retrospective nature of data extraction from medical records. To address this issue, we emphasised the need for standardised prospective documentation of fertility preservation

Table 4. Published studies reporting referral, fertility counselling, and fertility preservation rates in paediatric and adolescent cancer patients.

Study	Study design	Sample size, n ^a		Median age in years ^b (range)	Rate of fertility counselling (%) ^c	Rate of fertility preservation (%) ^d					
		Male	Female			Total	SP	TTC	OTC	OC	Other
Ben-Aharon <i>et al.</i> (2016)	Prospective survey cohort	–	62	13.2 (1.5–18.0)	n = 62/62 (NA) ^e	52 (84)	–	–	41	11	–
Lehmann <i>et al.</i> (2020)	Retrospective cohort study	99	53	NA (2.0–25.0)	n = 152/152 (NA) ^e	68 (45)	–	–	–	–	–
Kapadia <i>et al.</i> (2020)	Retrospective cohort study	82	–	16.0 (13.0–25.0)	n = 42/82 (51%)	29 (69)	29	–	–	–	–
Heritage <i>et al.</i> (2022)	Retrospective cohort study	67	55	NA	n = 91/122 (75%) • n = 19/91 by FS	75 (82)	35	1	2	2	27
Gregoire-Briard <i>et al.</i> (2022)	Retrospective cohort study	–	89	5.0 (3.0–13.0)	n = 29/89 (33%) • n = 12/29 by FS	11 (38)	–	–	–	1	10
Stukaite-Ruibiene <i>et al.</i> (2023)	Prospective survey cohort	NA	NA	NA (0.4–17.0)	n = 61/61 (NA) ^e • n = 6/61 by FS	3 (5)	3	–	–	–	–
Ligon <i>et al.</i> (2023)	Retrospective cohort study	91	58	NA	n = 90/149 (60%)	NA	–	–	–	–	–
Leavitt <i>et al.</i> (2024)	Prospective cohort study	27	27	5.0 (0.0–12.0)	n = 7/54 (13%)	6 (86)	–	3	3	–	–
Hartup <i>et al.</i> (2024)	Retrospective cohort study	35	23	Mean age 17.6 years (2.5–39.0)	n = 19/58 (33%) • n = 19/19 by FS	15 (79)	–	–	–	–	–
Grimes <i>et al.</i> (2024)	Retrospective cohort study	95	34	16.8 (NA)	n = 67/129 (52%)	29 (43)	–	–	–	–	–
McElhinney <i>et al.</i> (2024)	Retrospective cohort study	188	149	NA	n = 337/337 (NA) ^e	262 (78)	48	98	106	10	–
Corona <i>et al.</i> (2025)	Retrospective cohort study	103	69	8.0 (2.5–14.8)	n = 90/172 (52%)	58 (64)	20	16	19	3	–
Clasen <i>et al.</i> (2026)	Prospective cohort study	345	254	9.0 (0.0–23.0)	n = 396/599 (66.1%) • n = 396/396 by FS	238/396 (60.1)	78	30	113	2	15

^a None of the studies other than the current study reported how many patients were triaged at high risk of gonadal damage or otherwise.

^b Unless otherwise specified.

^c Unless otherwise specified, authors did not report who provided fertility counselling.

^d Unless otherwise specified, authors did not report which fertility preservation methods were pursued by patients.

^e All included patients were referred for fertility counselling. The authors did not disclose data on patients that were not referred, for which reason rates could not be accurately determined.

FS, fertility specialist; n, number of patients; NA, not available; OC, oocyte harvest and cryopreservation; OTC, ovarian tissue cryopreservation; SP, semen cryopreservation; TTC, testicular tissue cryopreservation.

counselling in HR^{gd} patients, including explicit recording of whether counselling was provided or whether fertility preservation was pursued, and when not provided or performed, the reasons for this decision. Improved documentation would facilitate more accurate evaluation of barriers to fertility preservation in future studies.

Previous studies in childhood cancer patients, survivors, and their families report that they highly prefer to receive (basic) fertility counselling at diagnosis, with the possibility to receive more detailed information after treatment has started and the initial shock and emotions of diagnosis have passed (Bath *et al.*, 2004; Clasen *et al.*, 2023). By providing patient-specific fertility information to all patients, miscommunication regarding fertility could be prevented, which may decrease future concerns and regrets regarding fertility and fertility preservation (Clasen *et al.*, 2023). Patients are reported to experience less psychosocial issues and a better quality-of-life after they have received fertility counselling, regardless of their personal anticipated risk of gonadal damage (Skinner *et al.*, 2006; Mulder *et al.*, 2021a,b,c; Clasen *et al.*, 2023).

The strength of this study is that it provides the results of 4 years of established oncofertility care in a national cohort of all childhood cancer patients, newly diagnosed and relapsed, male and female

patients. Compared to our previous study from 2021 (van der Perk *et al.*, 2021), we saw an increase in counselling and preservation rates in both newly diagnosed and relapsed HR^{gd} patients. However, we still did not reach 100% counselling and preservation rates. The limitation of this study is that a small subset of HR^{gd} patients during the establishment of oncofertility care in our centre may still not have been identified.

Conclusion

We conclude that standardised but personalised oncofertility care is valuable to identify childhood cancer patients at high risk for treatment-induced gonadal damage. Further improvement can be made regarding triage of all childhood cancer patients at diagnosis, combined with standard documentation of fertility risk and counselling, but also when treatment is intensified and at relapse, by continuous awareness of a patient's personal gonadal damage risk. In our expertise, a dedicated oncofertility care team is essential in that respect. Knowledge derived from future studies on the risks and benefits of cryopreservation procedures, as well as reports on reproductive outcomes (e.g. pregnancy and live birth rates) after and

the safety of cryopreservation and autotransplantation of gonadal tissue in larger cohorts will guide future development and improvement of oncofertility care strategies.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data cannot be shared for ethical and privacy reasons.

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Authors' roles

N.H.Z.C. contributed to the conception and design of the study, data acquisition, analysis and interpretation, and drafted the manuscript. M.E.M.v.d. P. contributed to the conception and design of the study and interpretation of data, and critically revised the manuscript. S.L.B. contributed to data analysis and interpretation, and critically revised the manuscript. J.v. L. contributed to data analysis and interpretation, and critically revised the manuscript. C.H.E.W. contributed to data analysis and interpretation, and critically revised the manuscript. I.M.I.J. contributed to data acquisition, analysis and interpretation, and critically revised the manuscript. J.R. contributed to data analysis and interpretation, and critically revised the manuscript. A.J.K. contributed to data analysis and interpretation, and critically revised the manuscript. A.L.F.v.d.K. contributed to data analysis and interpretation, and critically revised the manuscript. A.F.W.v.d.S. contributed to data analysis and interpretation, and critically revised the manuscript. S.J.C.M.M.N. contributed to data analysis and interpretation, and critically revised the manuscript. M.A.V. contributed to data analysis and interpretation, and critically revised the manuscript. A.M.E.B. contributed to data analysis and interpretation, and critically revised the manuscript. M.D.v.d.W. contributed to the conception and design of the study, data acquisition, analysis and interpretation, and critically revised the manuscript. M.M.v.d.H.-E. contributed to the conception and design of the study, data analysis and interpretation, and critically revised the manuscript. All authors approve the final version of the manuscript for publication and agree to be accountable for all aspects of the work.

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Disclosures

The authors have declared that no competing interests exist.

References

- Anazodo A, Laws P, Logan S, Saunders C, Travaglia J, Gerstl B, Bradford N, Cohn R, Birdsall M, Barr R *et al*. How can we improve oncofertility care for patients? A systematic scoping review of current international practice and models of care. *Hum Reprod Update* 2019; **25**:159–179.
- Bath LE, Tydeman G, Critchley HO, Anderson RA, Baird DT, Wallace WH. Spontaneous conception in a young woman who had ovarian cortical tissue cryopreserved before chemotherapy and radiotherapy for a Ewing's sarcoma of the pelvis: case report. *Hum Reprod* 2004; **19**:2569–2572.
- Ben-Aharon I, Abir R, Perl G, Stein J, Gilad G, Toledano H, Elitzur S, Avrahami G, Ben-Haroush A, Oron G *et al*. Optimizing the process of fertility preservation in pediatric female cancer patients—a multi-disciplinary program. *BMC Cancer* 2016; **16**:620.
- Botta L, Gatta G, Capocaccia R, Stiller C, Canete A, Dal Maso L, Innos K, Mihor A, Erdmann F, Spix C *et al*; EUROCARE-6 Working Group. Long-term survival and cure fraction estimates for childhood cancer in Europe (EUROCARE-6): results from a population-based study. *Lancet Oncol* 2022; **23**:1525–1536.
- Braye A, Tournaye H, Goossens E. Setting up a cryopreservation programme for immature testicular tissue: lessons learned after more than 15 years of experience. *Clin Med Insights Reprod Health* 2019; **13**: 1179558119886342.
- Clasen NHZ, van der Perk MEM, Neggers S, Bos AME, van den Heuvel-Eibrink MM. Experiences of female childhood cancer patients and survivors regarding information and counselling on gonadotoxicity risk and fertility preservation at diagnosis: a systematic review. *Cancers (Basel)* 2023; **15**:1946.
- Clasen NHZ, van der Perk MEM, van de Wetering MD, Bos AME, van der Kooi ALF, van Loon K, Veening MA, Im IJ, Neggers S, van Grotel M *et al*. Safety of laparoscopic oophorectomy in a Dutch national pediatric cancer cohort. *F S Rep* 2026; **7**:69–80.
- Corkum KS, Rhee DS, Wafford QE, Demeestere I, Dasgupta R, Baertschiger R, Malek MM, Aldrink JH, Heaton TE, Weil BR *et al*. Fertility and hormone preservation and restoration for female children and adolescents receiving gonadotoxic cancer treatments: a systematic review. *J Pediatr Surg* 2019; **54**:2200–2209.
- Corona LE, Bak M, Farje D, Rosoklija I, Kennedy T, Zarnegar-Lumley S, Lockart BA, Meyer T, Kamanzi S, Hirsch JA *et al*. Formal fertility preservation program facilitates equitable fertility care among pediatric oncology and stem cell transplant patients. *J Pediatr Surg* 2025; **60**:162400.
- Deshpande NA, Braun IM, Meyer FL. Impact of fertility preservation counseling and treatment on psychological outcomes among women with cancer: a systematic review. *Cancer* 2015; **121**:3938–3947.
- Dolmans MM, Luyckx V, Donnez J, Andersen CY, Greve T. Risk of transferring malignant cells with transplanted frozen-thawed ovarian tissue. *Fertil Steril* 2013; **99**:1514–1522.
- Dolmans MM, Marinescu C, Saussoy P, Van Langendonck A, Amorim C, Donnez J. Reimplantation of cryopreserved ovarian tissue from patients with acute lymphoblastic leukemia is potentially unsafe. *Blood* 2010; **116**:2908–2914.
- Duffin K, Neuhaus N, Andersen CY, Barraud-Lange V, Braye A, Eguizabal C, Feraille A, Ginsberg JP, Gook D, Goossens E *et al*. A 20-year overview of fertility preservation in boys: new insights gained through a comprehensive international survey. *Hum Reprod Open* 2024; **2024**:hoae010.
- Ellison LF, Xie L, Sung L. Trends in paediatric cancer survival in Canada, 1992 to 2017. *Health Rep* 2021; **32**:3–15.

- Emrich NLA, Einkenkel R, Farber CM, Schallmoser A, Sanger N. Ovarian tissue cryopreservation for fertility preservation: a two-decade single-center experience with 451 children and adolescents. *Reprod Biol Endocrinol* 2025;**23**:51.
- Fayomi AP, Peters K, Sukhwani M, Valli-Pulaski H, Shetty G, Meistrich ML, Houser L, Robertson N, Roberts V, Ramsey C *et al.* Autologous grafting of cryopreserved prepubertal rhesus testis produces sperm and offspring. *Science* 2019;**363**:1314–1319.
- Gillipelli SR, Pio L, Losty PD, Abdelhafeez AH. Female fertility cryopreservation outcomes in childhood cancer: a systematic review. *J Pediatr Surg* 2024;**59**:1564–1568.
- Goossens EVV, de Beer E, Delgouffe E, Mateizel I, Ernst C, Waelput W, Gies I, Tournaye H. First successful transplant of human immature testicular tissue after gonadotoxic therapy during childhood: complete spermatogenesis in intra-testicular grafts. medRxiv, <https://doi.org/10.64898/2026.03.04.26347483>, 2026, preprint: not peer reviewed.
- Gregoire-Briard F, Mitsakakis N, Hayawi L, Dumont T. Evaluation of fertility preservation counseling and treatments for female oncology patients in an urban pediatric Canadian center. *J Adolesc Young Adult Oncol* 2022;**11**:518–524.
- Grimes AC, Sugalski AJ, Nuno MM, Ramakrishnan S, Beauchemin MP, Robinson PD, Santesso N, Walsh AM, Wrightson AR, Yu LC *et al.* Clinical practice guideline-inconsistent management of fertility preservation in pediatric cancer patients in community settings: a children's oncology group study. *J Adolesc Young Adult Oncol* 2024;**13**:776–784.
- Hartup LA, Go VA, Robinson RD. Standardized reproductive endocrinology and infertility consultation for pediatric and adolescent oncology patients. *J Adolesc Young Adult Oncol* 2024;**13**:614–621.
- Heritage SR, Feast A, Mourad M, Smith L, Hatcher H, Critoph DJ. Documentation of oncofertility communication in adolescents and young adults with cancer: a retrospective analysis. *J Adolesc Young Adult Oncol* 2022;**11**:275–283.
- Hudson MM, Link MP, Simone JV. Milestones in the curability of pediatric cancers. *J Clin Oncol* 2014;**32**:2391–2397.
- Kapadia A, Shoureshi PS, Bash J, Jiang DD, Lindemulder S, Hedges J, Seideman CA. An institutional assessment of sperm cryopreservation and fertility counselling in pubertal male cancer survivors. *J Pediatr Urol* 2020;**16**:474.e1–474.e4.
- Khattak H, Malhas R, Craciunas L, Affi Y, Amorim CA, Fishel S, Silber S, Gook D, Demeestere I, Bystrova O *et al.* Fresh and cryopreserved ovarian tissue transplantation for preserving reproductive and endocrine function: a systematic review and individual patient data meta-analysis. *Hum Reprod Update*, 2022;**28**:400–416.
- Kourta D, Kanbar M, Amorim CA, Wyns C. Cancer cell contamination and decontamination methods for ovaries and testes: special focus on prepubertal gonads with a view to safe fertility restoration. *Hum Reprod* 2023;**38**:780–798.
- Leavitt AP, Albritton KH, Cazzell M, Stevenson E. Expansion of the fertility preservation program to all newly diagnosed prepubertal patients with cancer at a pediatric hospital. *J Pediatr Hematol Oncol Nurs* 2024;**41**:212–219.
- Lehmann V, Kutteh WH, Sparrow CK, Bjornard KL, Klosky JL. Fertility-related services in pediatric oncology across the cancer continuum: a clinic overview. *Support Care Cancer* 2020;**28**:3955–3964.
- Letourneau JM, Ebbel EE, Katz PP, Katz A, Ai WZ, Chien AJ, Melisko ME, Cedars MI, Rosen MP. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. *Cancer* 2012;**118**:1710–1717.
- Ligon JA, Hayashi M, Ciampa D, Kramer C, Guastella A, Fuchs RJ, Herati AS, Christianson MS, Chen AR. A multidisciplinary pediatric oncofertility team improves fertility preservation and counseling across 7 years. *Cancer Rep (Hoboken)* 2023;**6**:e1753.
- Martinez F; International Society for Fertility Preservation–ESHRE–ASRM Expert Working Group. Update on fertility preservation from the Barcelona International Society for Fertility Preservation–ESHRE–ASRM 2015 expert meeting: indications, results and future perspectives. *Fertil Steril* 2017;**108**:407–415.e11.
- McElhinney KL, McLean SK, Zarnegar-Lumley S, Laronda MM, Rowell EE. Comprehensive fertility preservation can be offered in a timely manner around gonadotoxic therapy in children and adolescents. *Pediatr Blood Cancer* 2024;**71**:e31232.
- Meacham LR, Ketterl TG, Bjornard KL, Nahata L, Gomez-Lobo V, Close AG, Rotz SJ, Dwiggins ML, Hoefgen HR, Kayiira A *et al.*; Leadership Committee of the Pediatric and Adolescent Committee of the Oncofertility Consortium. Pediatric and adolescent considerations for the revised ASCO guidelines. *J Clin Oncol* 2025;**43**:3134–3135.
- Mitchell RT, Eguizabal C, Goossens E, Grynberg M, Jahnukainen K, Le Clef N, Mulder CL, Neuhaus N, Rimmer MP, Stukenborg JB *et al.*; ESHRE FP for Boys Working Group. ESHRE good practice recommendations on fertility preservation involving testicular tissue cryopreservation in children receiving gonadotoxic therapies†. *Hum Reprod* 2025;**40**:1391–1431.
- Mulder RL, Font-Gonzalez A, Green DM, Loeffen EAH, Hudson MM, Loonen J, Yu R, Ginsberg JP, Mitchell RT, Byrne J *et al.*; PanCareLIFE Consortium. Fertility preservation for male patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol* 2021a;**22**:e57–e67.
- Mulder RL, Font-Gonzalez A, Hudson MM, van Santen HM, Loeffen EAH, Burns KC, Quinn GP, van Dulmen-den Broeder E, Byrne J, Haupt R *et al.*; PanCareLIFE Consortium. Fertility preservation for female patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol* 2021b;**22**:e45–e56.
- Mulder RL, Font-Gonzalez A, van Dulmen-den Broeder E, Quinn GP, Ginsberg JP, Loeffen EAH, Hudson MM, Burns KC, van Santen HM, Berger C *et al.*; PanCareLIFE Consortium. Communication and ethical considerations for fertility preservation for patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol* 2021c;**22**:e68–e80.
- Newton K, Howard AF, Thorne S, Kelly MT, Goddard K. Facing the unknown: uncertain fertility in young adult survivors of childhood cancer. *J Cancer Surviv* 2021;**15**:54–65.
- Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, Friedman DL, Marina N, Hobbie W, Kadan-Lottick NS *et al.*; Childhood Cancer Survivor Study. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 2006;**355**:1572–1582.
- Practice Committee of the American Society for Reproductive Medicine. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. *Fertil Steril* 2019;**112**:1022–1033.
- Practice Committee of the American Society for Reproductive Medicine. Fertility preservation in patients with medical indications: a committee opinion. *Fertil Steril* 2026;**125**:247–259.

- Reh AE, Lu L, Weinerman R, Grifo J, Krey L, Noyes N. Treatment outcomes and quality-of-life assessment in a university-based fertility preservation program: results of a registry of female cancer patients at 2 years. *J Assist Reprod Genet* 2011;**28**:635–641.
- Safrai M, Goossens E, Mitchell RT, Orwig KE, Mulder CL, van Pelt AMM, Gook DA, Feraille A, Delgouffe E, Ginsberg JP *et al*. Is the time right for transplanting immature testicular tissue or cells to restore male fertility? Expert perspectives on clinical implementation of auto-transplantation of cryopreserved testicular tissue or cells for fertility restoration. *Best Pract Res Clin Obstet Gynaecol* 2025;**102**:102638.
- Skaczkowski G, White V, Thompson K, Bibby H, Coory M, Orme LM, Conyers R, Phillips MB, Osborn M, Harrup R *et al*. Factors influencing the provision of fertility counseling and impact on quality of life in adolescents and young adults with cancer. *J Psychosoc Oncol* 2018;**36**:484–502.
- Skinner R, Wallace WH, Levitt GA; UK Children's Cancer Study Group Late Effects Group. Long-term follow-up of people who have survived cancer during childhood. *Lancet Oncol* 2006;**7**:489–498.
- Stukaite-Ruibiene E, van der Perk MEM, Vaitkeviciene GE, Bos AME, Bumbuliene Z, van den Heuvel-Eibrink MM, Rascon J. Evaluation of oncofertility care in childhood cancer patients: the EU-Horizon 2020 twinning project TREL initiative. *Front Pediatr* 2023;**11**:1212711.
- Su HI, Lacchetti C, Letourneau J, Partridge AH, Qamar R, Quinn GP, Reinecke J, Smith JF, Tesch M, Wallace WH *et al*. Fertility preservation in people with cancer: ASCO guideline update. *J Clin Oncol*, 2025;**43**:1488–1515.
- van der Perk MEM, van der Kooi ALF, van de Wetering MD, Ijgosse IM, van Dulmen-den Broeder E, Broer SL, Klijn AJ, Versluys AB, Arends B, Oude Ophuis RJA *et al*. Oncofertility care for newly diagnosed girls with cancer in a national pediatric oncology setting, the first full year experience from the Princess Maxima Center, the PEARL study. *PLoS One* 2021;**16**:e0246344.
- Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin* 2014;**64**:83–103.