Oncofertility outcomes in early-onset patients with non-breast solid malignancies: a systematic review

Natali Shirron,[a] Andrea Boutros,[c,d] Ithai Waldhorn,[a] Jubran Boulos,[a] Matteo Lambertini,[d,e] and Irit Ben-Aharon[a,b,*,e]

[a]Division of Oncology, Rambam Health Care Campus, Haifa, Israel
[b]Rappaport Faculty of Medicine, Technion, Haifa, Israel
[c]IRCCS Ospedale Policlinico San Martino, Genova, Italy
[d]Department of Internal Medicine and Medical Specialties (DIMI), School of Medicine, University of Genova, Genoa, Italy

eClinicalMedicine
2026;96: 103979

Published Online 4 June 2026
https://doi.org/10.1016/j.eclinm.2026.103979

Summary

Background The combination of a rising incidence of early-onset cancer and the trend towards delayed parenthood has made the impact of treatments on fertility highly significant. While there is abundant evidence on oncofertility outcomes of anti-cancer treatment protocols used in people with breast cancer and haematological malignancies, data regarding gonadal toxicity and fertility preservation in young people with other cancers are lacking. We aimed to systematically review gonadal toxicity, fertility outcomes, and preservation strategies in people with gastrointestinal, sarcoma, lung, and melanoma cancers.

Methods We conducted a systematic review following the PRISMA guidelines and searched PubMed, Embase, through June 1, 2025. Eligible studies included observational designs and case reports on gonadal function, fertility outcomes, or preservation strategies in adults with the selected cancers. Pregnancy-associated and pediatric studies were excluded. Two reviewers independently screened, extracted data, and assessed quality using the JBI tool. Formal assessment of publication bias as not undertaken, given the limited number of studies per outcome. Due to clinical and methodological heterogeneity, results were synthesised narratively. Heterogeneity was assessed using the I^2 statistic. The primary outcomes were treatment-related fertility impairment, including persistent amenorrhea or ovarian failure, return or maintenance of menses, and azoospermia and recovery of spermatogenesis at follow-up. Secondary outcomes included hormonal changes and reproductive outcomes such as pregnancy and live birth. This review was registered with PROSPERO (CRD42024557875).

Findings Of 3337 records screened, 102 studies were included, comprising 33 case-based publications (30 case reports and 3 case series) and 69 analytical studies, including 64 observational studies (6 prospective and 58 retrospective) and 5 other analytical designs. Evidence across studies was highly heterogeneous in design, treatment exposures, and outcome definitions. In melanoma, most survivors appear to retain fertility, though rare cases of immune checkpoint inhibitor-induced orchitis or azoospermia were observed. Sarcoma regimens with alkylating and platinum agents appear to carry the highest risk of persistent gonadal failure in both sexes, with partial sperm recovery possible in some cohorts. In gastrointestinal cancers, chemotherapy-induced gonadal dysfunction was often transient in younger patients, whereas pelvic radiotherapy resulted in near-universal ovarian failure and long-term male hypogonadism. In lung cancer, platinum-based regimens were associated with to premature menopause and endocrine disruption, yet fertility counselling and preservation were rarely provided. Exploratory meta-analyses suggested that pooled estimates were imprecise and limited by substantial heterogeneity.

Interpretation Gonadal toxicity risk varies by cancer type and treatment, while there is a paucity of robust evidence for the impact on malignancies that are emerging in the young population. Future prospective evaluation of gonadal function in the setting of early-onset cancer, as well as adequate evaluation of strategies to preserve fertility and minimise gonadal toxicity, is warranted.

Funding No external funding was received for this work. This study received internal institutional support.

*Corresponding author. Division of Oncology, Rambam Health Care Campus, Haifa, Israel.
E-mail address: I_Benaharon@rambam.health.gov.il (I. Ben-Aharon).
[e]Equal contribution.

Keywords: Oncofertility; Fertility preservation; Gonadal toxicity; Early onset cancer

Research in context

Evidence before this study

We searched PubMed and Embase from database inception to June 1, 2025, using terms related to cancer, fertility, and treatment-related gonadal toxicity, with no language restrictions, and identified 3337 records. Existing evidence on fertility outcomes in patients with non-breast solid malignancies is limited and heterogeneous. Most available studies are retrospective, include small sample sizes, and rely on surrogate markers such as hormonal levels rather than clinically meaningful reproductive outcomes. Evidence across cancer types has been fragmented, and a comprehensive synthesis of gonadal toxicity and fertility outcomes in these malignancies has been lacking.

Added value of this study

This systematic review provides a comprehensive synthesis of gonadal toxicity and fertility outcomes across melanoma, sarcoma, gastrointestinal, and lung malignancies in young patients. By systematically integrating evidence from 102 studies, this work identifies patterns of treatment-related gonadal risk across tumour types. In gastrointestinal cancers, ovarian dysfunction following chemotherapy appears frequently transient, whereas pelvic radiotherapy is consistently associated with markedly higher rates of ovarian failure. Evidence from male cohorts suggests that spermatogenic impairment may occur after cytotoxic therapy but can be partially reversible over time. This study also highlights major evidence gaps, including limited prospective data and inconsistent reporting of clinically meaningful reproductive outcomes.

Implications of all the available evidence

Across these malignancies, fertility risk appears to be driven primarily by treatment exposure rather than tumour type. Pelvic radiotherapy and highly gonadotoxic chemotherapy regimens represent the greatest threats to long-term gonadal function. Early fertility counselling and referral for fertility preservation should therefore be prioritised for patients at risk. Future research should focus on prospective studies with standardised fertility outcomes to better inform survivorship care and clinical guidelines.

Introduction

The incidence of cancer in the young population has been rising worldwide, with epidemiological studies indicating a 79% increase in the incidence of early-onset cancer from 1990 to 2019.[1,2] This emerging phenomenon, along with improved survival and the trend of delayed childbearing age, has significantly raised the impact of treatments on future fertility as a key issue for young patients with cancer.[3,4] Studies conducted on the population of Adolescents and Young adults (AYAs, which is defined as the age range 20–39 years) have suggested that concerns regarding treatment-related infertility are associated with emotional distress and poor quality of life (QoL), especially among women, who are anxious about entering treatment-related early menopause.[5,6] The term "oncofertility", coined in 2006, established a multidisciplinary interface between reproductive endocrinology/gynaecology and oncology, increasing oncologists' awareness of the need for fertility preservation.[7] Besides fertility, treatment-induced gonadal toxicity encompasses other hormonal-related domains that may be altered by treatment-induced gonadal toxicity, e.g., neurocognitive, cardiovascular, and psychosocial domains, including body image and sexuality, which also represent an issue for young patients with cancer.

Several factors greatly affect the impact of anticancer treatments on gonadal function: age is a key factor in female patients with cancer, while the risk of gonadal toxicity increases in older patients; the type of chemotherapy, as well as the dose and duration of treatment.[8–10] There is a paucity of data on the effects of newer biological agents and immunotherapies on the gonads.[11]

A major drawback in assessing gonadal function is the heterogeneity of data due to inconsistent use of anti-Mullerian hormone (AMH) as a standard surrogate biomarker across studies evaluating reproductive outcomes in young women with cancer.[12] Several fertility preservation options are available for young female patients. Established strategies include embryo and oocyte cryopreservation, which are considered standard-of-care and require controlled ovarian stimulation before gonadotoxic therapy. Ovarian tissue cryopreservation has emerged as a viable alternative, particularly in prepubertal girls or when treatment must begin urgently, with increasing reports of successful transplantation and live births.[13] Other surgical approaches, such as ovarian transposition and uterine fixation before pelvic irradiation, can help reduce radiation exposure.[14] More recently, uterine transposition has been described in selected patients requiring pelvic irradiation, aiming to preserve not only ovarian but also uterine function for future gestation.[15] In male patients, treatment-related testicular toxicity is derived mainly due to the effect on spermatogonial cells.[16,17] Detailed lists of chemotherapeutic agents (including alkylating compounds) and irradiation, and their effect on

different spermatogenic germ cell types, have been extensively reviewed.[16,18] The majority of chemotherapeutic drugs are given as part of multi-agent therapy; therefore, it can be difficult to ascertain the specific gonadal effect of each agent. Several agents have been found to exert gonadotoxic effects on males, such as alkylating and platinum-based agents. The effects are dose-dependent, but host-related factors might contribute to gonadal toxicity. Immunotherapies and targeted drugs can also directly impair male fertility. With immune checkpoint inhibitors (ICIs), reports include orchitis, impaired spermatogenesis, and azoospermia, although available data remain limited.[11] Radiation-induced testicular toxicity is a known effect, whereas a single dose as low as 2–3 Gy can induce azoospermia, and >6 Gy may lead to permanent azoospermia.[19] Total body irradiation involving exposure to 10–13 Gy has been shown to cause azoospermia in 85% of men, with oligozoospermia reported in the remaining patients. It is primarily due to direct damage to the testis.[20] Cryopreservation of semen before the start of chemotherapy or radiotherapy is an extremely effective means of fertility preservation for men and post-pubertal boys, as well as testicular shielding during radiation.[4] Ultimately, the eventual recovery of sperm production depends on the survival of the spermatogonial stem cells, their regeneration and differentiation capacity, and may take up to 2 years post-treatment in case of a reversible effect.

Guidelines for fertility preservation in young patients diagnosed with cancer have been issued by the European Society of Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) and incorporated into the standard of care.[21] Nevertheless, current guidelines rely on clinical evidence obtained mostly in the setting of breast cancer and haematological malignancies. In contrast, there is a lack of data regarding other malignancies, in which treatment protocols differ. Studies indicate that in these malignancies, oncofertility perspectives are less discussed, though warranted.[22,23]

Standard fertility preservation techniques, such as sperm, oocyte, and embryo cryopreservation, remain the mainstay of clinical practice. Reports on successful use following ovarian tissue cryopreservation are increasing, though they still cannot replace standard FP options. The role of gonadotropin-releasing hormone agonists for ovarian preservation has been studied mainly in the setting of breast cancer and haematological malignancies, indicating conflicting results.[24]

Recent data indicate an increase in the incidence of cancer in young adults, particularly in those under 40 years of age, with marked rises reported for colorectal cancer, lung cancer, and melanoma over the last two decades.[25–27] While current FP guidelines reflect evidence obtained mainly in the setting of breast cancer and haematological malignancies, there is a paucity of data regarding treatment protocols used for other cancer types. This systematic review aims to comprehensively evaluate the current state of oncofertility research and practice for patients with cancers other than breast malignancies. By synthesising existing evidence on fertility-preservation techniques, outcomes, and patient perspectives, this systematic review seeks to identify knowledge gaps and propose future directions for research and clinical care for young patients with cancer.

Methods

This systematic literature review was performed at the Joseph Fishman Oncology Center at Rambam Health Care Campus, Israel, and at the San Martino Hospital—University of Genova, Italy, between February and August 2025. The protocol of this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration code CRD42024557875). The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The Participants-Intervention/Exposure-Comparison-Outcomes (PICO) structure was used to perform the review.

The objective of this review was to examine the risk of treatment-induced gonadotoxicity in patients with gastrointestinal (GI), sarcoma, lung, or melanoma cancer. Primary outcomes for females included persistent amenorrhea or ovarian failure following treatment and the return or maintenance of menses. For males, primary outcomes included treatment-related azoospermia and recovery of spermatogenesis at follow-up. Secondary outcomes included hormonal changes and reported fertility outcomes such as pregnancy or live birth.

Search strategy and selection criteria

The keywords and research strings are reported in the Supplementary Appendix. Inclusion criteria were prospective and retrospective observational studies and case reports or case series conducted in adult patients.

We focused this review on commonly used therapies for gastrointestinal/sarcoma/lung, and melanoma cancers, as these malignancies serve as representative models for other solid tumours treated with similar regimens and associated adverse effects. We also excluded studies that concerned pregnancy-associated cancers, those on cancer survivors aged less than 18 (during treatment), and articles citing infertility without stating specific prevalence of outcome or risk data available. However, substantial variation in age distribution within adult cohorts was observed and considered a potential contributor to heterogeneity.

The negative filters in the databases were limited to full-text studies, reviews, systematic reviews, and meta-analyses. Articles resulting from the search were

screened and selected independently by 2 reviewers. In case of doubt about eligibility among the reviewers, a third author was asked to assess the eligibility criteria to resolve the disagreement. For non-selected articles, reviewers tracked the reason for exclusion only for studies assessed in full text. Sex-specific outcomes were extracted and analysed where reported; gender identity was not assessed in the included studies.

Search terms utilised across all electronic databases

The search terms target various aspects of infertility and reproductive health, including "infertility," "aspermia," "azoospermia," "gonadal toxicity," "pregnancy outcome," "ovarian reserve," and "fertility preservation." These terms are combined with cancer-specific keywords such as "melanoma," "sarcoma," "lung neoplasms," and "gastrointestinal cancer." Boolean operators (AND/OR) were applied to refine search queries across databases.

Data extraction and quality assessment

Trials that met the inclusion criteria were assessed for methodological quality by two authors (NS and IBA for gastrointestinal cancer; NS and GB for lung cancer; NS and AB for melanoma; NS and IW for sarcoma). The same two authors independently extracted the data from publications of included trials. The data extraction was discussed, and decisions were documented. Disagreements were resolved through consensus discussion. In the case of multiple publications for the same trial, the most up-to-date one was extracted. Data were extracted into a Microsoft Excel spreadsheet by the reviewers (variable strings are provided in the Supplementary Appendix). Extracted variables included demographic characteristics (e.g., age and sex), cancer type, treatment exposures (chemotherapy, radiotherapy, immunotherapy), and reproductive outcomes (hormonal markers, amenorrhea, azoospermia, pregnancy, and live birth). Extracted variables included demographic characteristics (e.g., age and sex), cancer type, and treatment exposures (chemotherapy, radiotherapy, and immunotherapy). Outcomes were categorised as surrogate (e.g., AMH, inhibin-B, hormonal markers) or clinically meaningful (e.g., amenorrhea, pregnancy, live birth, azoospermia, menstrual recovery). Given substantial clinical and methodological heterogeneity in patient populations, treatment exposures, follow-up durations, and outcome definitions, findings were primarily synthesised narratively. Where sufficient data were available, numerators and denominators were extracted to allow exploratory quantitative synthesis.

Risk of bias and quality assessment

Two reviewers independently assessed the methodological quality of all included studies using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists, selecting the appropriate tool for each study design (cohort, case–control, cross-sectional, case series, or case report). Each checklist item was rated as "Yes", "No", "Unclear", or "Not applicable". Disagreements were resolved by discussion or consultation with a third reviewer. An overall risk-of-bias judgement (low, moderate, or high) was assigned to each study based on the pattern of responses across items. The completed JBI appraisal forms are provided in the Supplementary Appendix. Formal assessment of publication bias was not performed due to the limited number of studies per outcome; potential reporting bias is therefore considered narratively. The certainty of the evidence was not formally graded (e.g., using GRADE) due to substantial clinical and methodological heterogeneity across studies.

Quantitative synthesis (meta-analysis)

Given substantial variability in study populations, treatment regimens, and outcome definitions, quantitative synthesis was restricted to outcomes reported in sufficiently comparable cohorts, defined by consistent outcome definitions and broadly similar treatment exposures. The following outcomes were quantitatively synthesised: persistent amenorrhea (gastrointestinal cancers), return of menses following treatment, and azoospermia after chemotherapy.

These meta-analyses were conducted as exploratory analyses and are presented in the Supplementary Appendix due to the substantial clinical and methodological heterogeneity across studies.

Statistical analysis

Meta-analyses were conducted using random-effects models, specified a priori to account for expected clinical and methodological heterogeneity. Proportions were pooled using a logit transformation, with study-level confidence intervals calculated using Wilson's score method. Pooled estimates were generated using restricted maximum likelihood (REML) as the primary estimator; DerSimonian–Laird estimates were computed for comparison and yielded similar results.

Between-study heterogeneity was assessed using Cochran's Q statistic and the I^2 statistic, interpreted as low (<25%), moderate (25–50%), substantial (50–75%), and high (>75%).

Where sufficient data were available, subgroup analyses were conducted by cancer site (colon, rectal, colorectal cancer, or mixed gastrointestinal), treatment exposure, and biological sex. These analyses were considered exploratory due to the limited number of studies within subgroups.

For outcomes reported by a single study (e.g., azoospermia risk following cisplatin vs. non-cisplatin regimens), results were presented descriptively with corresponding 95% confidence intervals rather than pooled estimates.

All statistical analyses were performed using Python (version 3.12), with the statsmodels, NumPy, and SciPy

libraries. Formal assessment of publication bias was not performed due to the limited number of studies per outcome. The literature search, conducted up to June 1, 2025, identified 3337 records from two databases: 2572 from PubMed and 765 from Embase (Fig. 1). Among them, 946 publications were considered potentially relevant (melanoma, sarcoma, gastrointestinal cancers, lung). After full-text review, 833 publications were excluded. Data extraction was performed across 102 publications; among them, 33 were case-based (30 case reports and 3 case series), 64 were observational studies (6 prospective and 58 retrospective), and the remaining studies comprised registry-based or mixed-design analyses. A summary of the characteristics of the included studies is provided in Table 1. The geographic distribution of included studies is illustrated in Supplementary Fig. S1, demonstrating predominance of studies from North America, Europe, and East Asia, with limited representation from low- and middle-income regions.

The main reasons for exclusion at full-text review included studies of benign tumours, absence of oncological treatment, lack of fertility-related outcomes, mixed disease populations without extractable data, and absence of patient-level data.

Ethics

This study was a systematic review of published data; therefore, ethical approval and informed consent were not required.

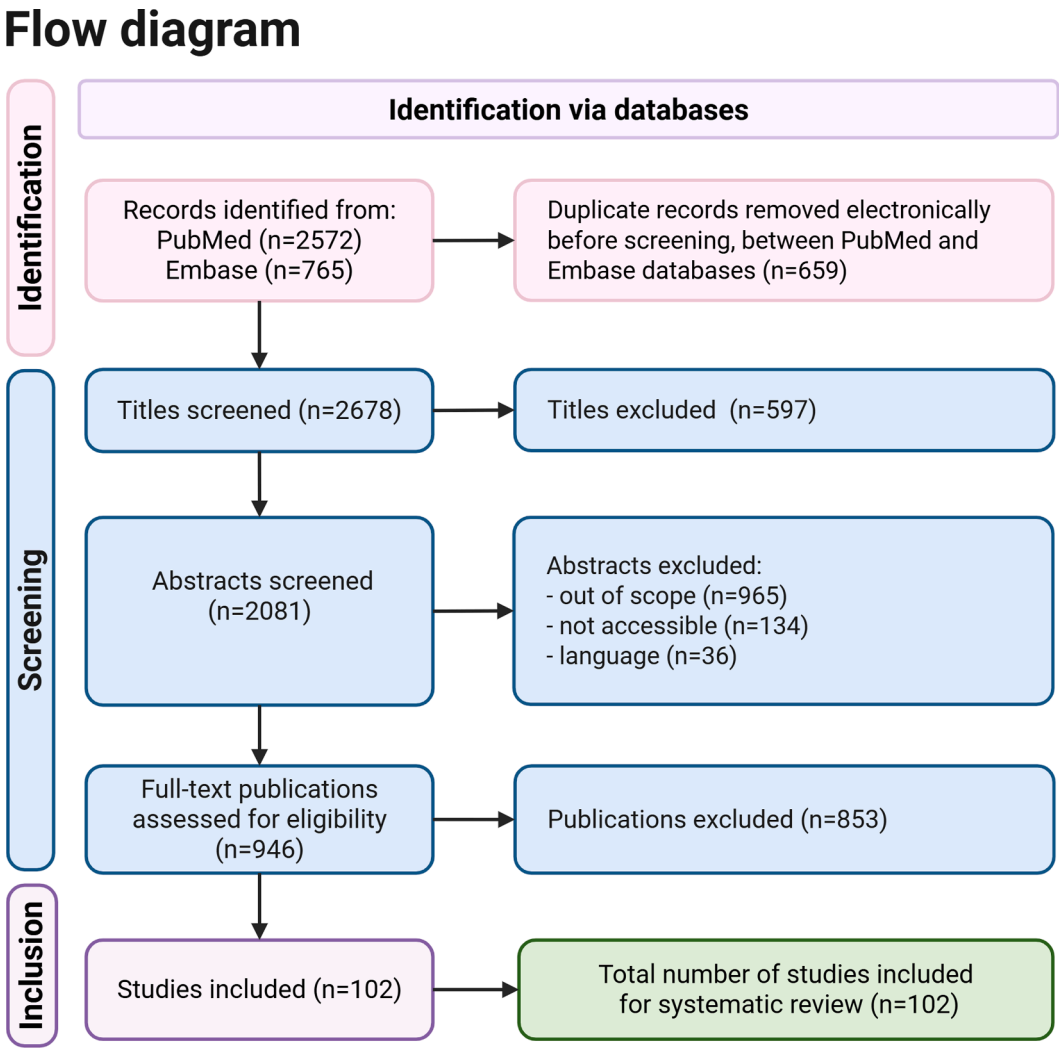

***Fig. 1:* PRISMA flow diagram of study selection.** Flow diagram illustrating the process of study identification, screening, eligibility assessment, and inclusion. A total of 3337 records were identified through database searching (PubMed and Embase), of which 659 duplicates were removed. Following title and abstract screening, 946 full-text articles were assessed for eligibility, and 102 studies were ultimately included in the systematic review. Reasons for exclusion at each stage are detailed within the figure. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Characteristic	Value
Total studies	102
Case reports/case series	33
Analytical studies	69
Observational studies	64
Prospective	6
Retrospective	58
Other analytical designs[a]	5
Cancer types represented[b]	
Gastrointestinal cancers	40
Sarcoma	39
Melanoma	13
Lung cancer	10
Outcomes evaluated[c]	
Female gonadal function/menstrual outcomes	Reported
Male gonadal function/semen outcomes	Reported
Fertility preservation strategies	Reported
Pregnancy/live birth outcomes	Reported
Study population	Mixed adult and AYA populations

Summary of study designs, populations, and outcomes across the 102 studies included in this systematic review, stratified by study type and cancer group. AYA = adolescents and young adults. [a]Other analytical designs include registry-based studies, cross-sectional cohorts, and mixed-methods analyses. [b]Cancer categories are not mutually exclusive; some studies included multiple malignancies. [c]Outcome categories are not mutually exclusive; individual studies frequently reported more than one fertility endpoint.

Table 1: **Characteristics of included studies.**

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of the included studies, 13 investigated melanoma, 39 sarcoma, 40 gastrointestinal cancers, and 10 lung cancer. To improve interpretability, studies were organised according to outcome.

Given substantial heterogeneity in patient characteristics, treatment exposures, study designs, and outcome definitions, a primarily narrative synthesis was undertaken. Exploratory meta-analyses were conducted for selected outcomes where sufficient comparability existed, but pooled estimates should be interpreted with caution due to the underlying clinical and methodological variability. Exploratory meta-analyses showed that pooled estimates were imprecise and accompanied by substantial heterogeneity across studies ($I^2 > 75\%$ in all pooled outcomes), including variability in treatment regimens, exposure to pelvic radiotherapy, and follow-up duration (Supplementary Figs. S2–S4).

Detailed study characteristics and outcomes across cancer types are presented in Tables 2–9.

Melanoma

Male gonadotoxicity

Literature search yielded several studies indicating various treatment-related male gonadal effects ranging from hormonal alterations to infertility, particularly due to immune checkpoint inhibitors (ICI) and interferon therapy, although the number of cases is small. Male gonadal function and reproductive outcomes in melanoma are summarised in Table 2. A cross-sectional study found that 4 out of 22 melanoma patients on ICI therapy had abnormal semen parameters. However, three cases involved confounding factors such as radiotherapy, prior chemotherapy, and alcohol abuse.[28] Case reports further highlighted the potential risk of treatment-induced azoospermia. In one case, a 30-year-old melanoma patient developed azoospermia two years after initiating ICI therapy, while a testicular biopsy revealed inflammatory infiltrates and a Sertoli-cell-only histological pattern.[29] This pattern was also described in a case following interferon therapy.[30]

Hormone-related alterations have been described in a few publications. A prospective case series assessing inhibin B levels in 12 male melanoma patients before and after one year of low-dose interferon alpha therapy found no significant differences, suggesting that this treatment does not significantly impair endocrine function related to male fertility.[31] However, a study by Ghezzi et al. examining sperm quality and DNA integrity in two patients found that one patient experienced a significant reduction in total sperm count and motility, along with increased DNA fragmentation. At the same time, testosterone and luteinizing hormone levels remained within normal ranges.[32]

Despite evidence of potential gonadotoxicity, long-term fertility outcomes in melanoma survivors may not be significantly impaired. A large cohort study involving 1453 melanoma cases found no significant differences in post-cancer pregnancy rates between melanoma survivors and controls.[33] These findings suggest that while certain therapies, particularly ICIs and interferon, may cause sperm abnormalities or azoospermia, the overall impact on reproductive potential varies.

Notably, a prospective observational study of 26 male melanoma patients treated with ICIs, specifically designed to assess testicular function, found a modest, non-significant reduction in sperm output and increased FSH levels overall, with one patient developing persistent azoospermia consistent with autoimmune orchitis.[34]

Melanoma

Female gonadal toxicity

Studies evaluating female fertility outcomes in melanoma survivors indicate a variable degree of treatment-induced ovarian toxicity. Ovarian function and reproductive outcomes in melanoma are detailed in

No	Ref	Type of study	Median age	Participants	Anticancer Treatment(s)	Results
1	Salzmann et al. 2021[29]	Cross-sectional pilot study (single-centre)	49	25	Immune checkpoint inhibitors (ICIs—PD-1/PD-L1 and/or CTLA-4 inhibitors)	Most patients (82%) had normal semen parameters; a few developed azoospermia or other sperm abnormalities (often with confounders like prior chemo/radiation). One patient with normal pre-treatment sperm became azoospermic ~1 year after ICI therapy, with evidence of an inflammatory immune orchitis. Overall, ICIs generally spare fertility in most men, but rare immune-mediated loss of spermatogenesis may occur.
2	Rabinowitz et al. 2021[30]	Case report	30	1	Combination immune checkpoint inhibitor therapy (ipilimumab + nivolumab)	Azoospermia, testicular biopsy shows an inflammatory infiltrate and Sertoli-only pathology
3	Longo et al. 2002[31]	Case report	38	1	Interferon-α immunotherapy (adjuvant interferon-alpha for melanoma)	Azoospermia, still azoospermia after 1 year of cessation
4	Karamfilov et al. 2000[32]	Prospective cohort study	54 (range 28–28)	12	Adjuvant low-dose interferon-α2b (3 million IU thrice weekly for 1 year)	Mean serum inhibin B before interferon- 225.4 ± 112.5 pg/ml Mean after interferon 229.6 ± 82 pg/ml ($p > 0.05$) Mean serum inhibin B controls 201.5 ± 17.1 pg/ml ($p > 0.05$) The study concluded that low-dose IFN-α did not adversely affect male fertility in this cohort.
5	Ghezzi et al. 2020[33]	Case report (two cases)	36 and 39 years	2	Targeted therapy with BRAF ± MEK inhibitors—Case 1: vemurafenib (BRAF inhibitor); Case 2: dabrafenib (BRAF inhibitor) + Trametinib (MEK inhibitor)	Case 1 (vemurafenib)—maintained normal sperm count and DNA integrity after treatment, and his partner conceived naturally, leading to a full-term healthy birth. FRONTIERSIN.ORG . Case 2 (dabrafenib + trametinib)—at follow-up had oligoasthenospermia (low count/motility) and increased sperm DNA fragmentation. Natural conception was not achieved; assisted reproductive techniques were recommended. Vemurafenib had no obvious gonadotoxic effect, whereas dabrafenib + trametinib was associated with impaired sperm quality.
6	Stensheim et al. 2011[34]	Retrospective cohort study	34	27,556 (1453 Melanoma)	**Various standard therapies** (surgery, chemotherapy, radiotherapy, etc., as appropriate per cancer type—not detailed in report)	Examined post-treatment pregnancy rates. Overall, cancer survivors had significantly lower chances of pregnancy compared to age-matched controls. Fertility impact varied by cancer: survivors of melanoma or thyroid cancer had no difference vs. controls.
7	Boutros et al. 2025[35]	Prospective mixed longitudinal cross-sectional cohort	26	Melanoma	Immune Checkpoint Inhibitors (for melanoma), no prior chemo/radiotherapy	One case (≈4%) developed persistent azoospermia with autoimmune orchitis. Median sperm output fell ~34%, sperm concentration ~30%, but these declines were not statistically significant (especially after excluding the orchitis case). LH & testosterone stable; FSH rose but not significantly after exclusion.

Summary of studies reporting treatment-related effects on gonadal function and reproductive outcomes in male patients with melanoma, including semen parameters, hormonal markers, and clinical fertility outcomes across different therapeutic exposures. ICI = immune checkpoint inhibitor; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; CTLA-4 = cytotoxic T-lymphocyte–associated protein 4; BRAF = B-Raf proto-oncogene; MEK = mitogen-activated protein kinase kinase; FSH = follicle-stimulating hormone; LH = luteinising hormone.

Table 2: **Gonadal function and reproductive outcomes in male patients with melanoma.**

Table 3. A cohort study analysed 21,666 adolescent and young adult (AYA) cancer survivors, including 2953 melanoma cases, and found that the mean age at premature ovarian insufficiency (POI) diagnosis was 34.6 years. The adjusted relative risk of POI was 0.97 for patients aged 15–29 years and 1.10 for those aged 30–39 years, compared with cancer-free individuals, after adjusting for age, income, parity, and immigration status.[35] Similarly, a cohort study of 14,316 AYA cancer survivors, including 2181 melanoma cases, reported an adjusted relative risk of infertility diagnosis of 1.17, suggesting a slight increase in infertility risk.[36]

Despite concerns about fertility, case reports, and cohort studies indicate that melanoma survivors can achieve successful pregnancies. Bucheit et al. reported a case of a 32-year-old melanoma patient who spontaneously conceived and delivered healthy dichorionic twins while treated with ipilimumab and nivolumab treatment.[37] This patient had a history of extensive prior treatments, including neck radiotherapy, chemotherapy, IL-2, Vemurafenib, Cobimetinib, and Atezolizumab. Larger cohort studies further support these findings: a study of 42,691 female melanoma survivors found that standardised birth ratios (SBRs) were comparable to those in the general population.[38] Similarly, Stensheim et al. examined pregnancy rates among 27,556 cancer survivors, including 2495 melanoma cases, and found no significant difference in pregnancy rates between melanoma survivors and matched controls. A prospective biomarker analysis of young women receiving adjuvant ipilimumab demonstrated a significant decline in anti-Müllerian hormone (AMH)

No.	Ref	Type of study	Median age	Participants	Anticancer Treatment(s)	Results
1	Flatt et al. 2023[36]	Retrospective, cohort study	31.4	21,666 (2953 Melanoma)	Not specified	Adolescent and young adult (AYA) cancer survivors. Adjusted relative risks of POI stratified by age group: 15–29 years –0.97 (0.68, 1.39) 30–39 years 1.10 (0.97, 1.54) * Adjusted for age, income, parity before cancer diagnosis, and immigration status, compared to matched cancer-free individuals
2	Velez et al. 2021[37]	Retrospective, cohort study	33	14,316 (2181 Melanoma)	Not specified	Adolescent and young adult (AYA) cancer survivors. The adjusted relative risk of infertility diagnosis was: 1.17 (95% CI: 1.01–1.35, p = 0.03)
3	Bucheit et al. 2020[38]	Case report	32	1	Multiple treatments, including: –Chemotherapy–Radiotherapy–Interleukin-2 (IL-2)–BRAF inhibitors (vemurafenib)–MEK inhibitors (Cobimetinib)–Immune checkpoint inhibitors (Ipilimumab + Nivolumab)–Anti-PD-L1 therapy (Atezolizumab)	A 32-year-old female with metastatic melanoma received various treatments over time. Notably, she spontaneously conceived and delivered healthy dichorionic twins during induction therapy with ipilimumab and nivolumab, followed by maintenance nivolumab.
4	Hartman et al. 2013[39]	Retrospective, cohort study	NA (<45)	42,691 (4637 Melanoma)	Not specified	Melanoma skin cancer survivors had standardised birth ratios (SBRs), indicating they were as likely to give birth as the general population.
5	Stensheim et al. 2011[34]	Retrospective, cohort study	32	27,556 (2495 Melanoma)	Not specified	This study reported that pregnancy rates among cancer survivors did not differ significantly from those of controls, particularly for survivors of malignant melanoma.
6	Buchbinder et al. 2006[41]	Prospective cohort (biomarker analysis; ECOG-ACRIN E1609)	28	28	Adjuvant ipilimumab (CTLA-4 inhibitor)	Significant decline in AMH following treatment (dropped from 4.24 ng/mL before treatment to 3.51 ng/mL after treatment, p-value of <0.001), suggesting potential reduction in ovarian reserve despite preserved menstrual function; findings indicate possible subclinical ovarian toxicity.

Summary of studies reporting treatment-related effects on ovarian function and reproductive outcomes in female patients with melanoma, including measures of ovarian reserve, infertility risk, and pregnancy outcomes across different treatment exposures. AYA = adolescents and young adults; POI = premature ovarian insufficiency; AMH = anti-Müllerian hormone; CI = confidence interval; CTLA-4 = cytotoxic T-lymphocyte–associated protein 4; PD-L1 = programmed death-ligand 1; ECOG = Eastern Cooperative Oncology Group.

Table 3: **Gonadal function and reproductive outcomes in female patients with melanoma.**

levels following treatment, suggesting potential subclinical impairment of ovarian reserve despite the absence of reported clinical infertility outcomes.[39,40]

Overall, current evidence suggests that a mild gonadotoxic profile for melanoma treatment, as many survivors retain fertility and achieve pregnancies comparable to the general population. However, the long-term reproductive impact of newer therapies, such as immune checkpoint inhibitors and targeted agents, remains insufficiently understood and warrants further prospective investigation.

Sarcoma

Male gonadal toxicity

Studies on male gonadal toxicity in sarcoma and osteosarcoma patients showed significant chemotherapy-induced fertility impairment, with high rates of azoospermia and oligospermia. Male fertility and gonadal outcomes in sarcoma are presented in Table 4. Chemotherapeutic agents, particularly cisplatin and ifosfamide, were identified as major contributors to long-term testicular dysfunction.[41] A study in osteosarcoma patients revealed that 12 of 14 patients developed oligo- or azoospermia post-chemotherapy, with high-dose ifosfamide being a key factor.[42] Similarly, it was reported that 10 out of 18 osteosarcoma patients developed azoospermia, with those receiving cisplatin being mostly affected.[43]

Despite severe acute gonadal toxicity, some degree of sperm recovery was observed. Mesitrich et al. noted that while nearly all osteosarcoma patients became azoospermic during PADIC chemotherapy (cisplatin, doxorubicin, dacarbazine), sperm production resumed in 30 of 32 men after two years, with 78% achieving sperm counts above 10 million/ml. However, recovery was significantly lower in those receiving cisplatin doses $\geq$600 mg/m^2.[17]

Surgical sperm retrieval techniques have yielded limited success in chemotherapy-induced azoospermia.[44] Found that among five patients undergoing MD-TESE post-chemotherapy, sperm were retrieved in only three, despite all exhibiting Sertoli cell-only syndrome. Similarly, micro-TESE studies by reported retrieval rates of 0% and 14%, respectively, highlighting the challenge of fertility preservation after chemotherapy.

Radiotherapy further exacerbates gonadal toxicity.[45] reported that among 26 patients treated with chemotherapy, those receiving additional abdominal or thigh radiotherapy developed decreased testicular size,

No.	Ref	Type of study	Median age	Participants	Cancer Treatment(s)	Outcome	Results
1	Hibi et al. 2007[45]	Retrospective, cohort study	NA	5 (2 sarcoma)	Chemotherapy regimens including: –Cisplatin (CDDP)–Mitomycin C (MMC)–Vincristine (VCR)–Adriamycin (ADR)–Ifosfamide (IFM)	MD-TESE post-chemotherapy	All patients with Sertoli cell-only syndrome, sperm retrieved in 3 out of 5 patients.
2	Longhi et al. 2003[43]	Retrospective, cohort study	25 years (only for the range 18–37)	14 osteosarcomas	Chemotherapy, with 9 out of 14 patients receiving high-dose ifosfamide	Sperm cryopreservation post-chemotherapy	12 out of 14 patients showed oligo- or azoospermia. Amongst the 12 patients, 9 received high-dose ifosfamide.
3	Siimes et al. 1990[44]	Retrospective, cohort study	NA	18 osteosarcomas	Chemotherapy, including regimens with and without cisplatin	Sperm quality and testis volume after chemo	Testicular volume was reduced in 13 patients. Among 17 patients who provided semen samples: –10 were azoospermic–2 were oligozoospermic. Testicular volume and sperm count were associated with the type of chemotherapy. Of the 7 patients who received cisplatin-containing chemotherapy, 6 had small testes and azoospermia; 1 was oligozoospermic with normal-sized testes. In 3 of the 11 patients whose chemotherapy did not include cisplatin, testicular size and sperm count were normal.
4	Meistrich et al. 1989[17]	Retrospective, cohort study	NA	32 osteosarcomas	PADIC chemotherapy regimen: –Cisplatin–Adriamycin (doxorubicin)–Dacarbazine	Sperm quality after PADIC chemotherapy	Semen volume was not affected, and sperm motility was reduced only during treatment. Although nearly all patients were rendered azoospermic during treatment, sperm production resumed in 30 of 32 patients examined at least 2 years after treatment. In 78% of treated men, sperm counts will return to more than 10 million/ml. The percentage of men whose sperm counts recovered to normal was lower for those receiving cisplatin dosages greater than or equal to 600 mg/m^2
5	Shamberger, Sherins, and Rosenberg 1981[46]	Retrospective, cohort study	38.6	26	Chemotherapy regimens including: –Doxorubicin–Cyclophosphamide–High-dose methotrexate, with or without radiotherapy	Sperm quality after chemotherapy and radiotherapy	Among the 5 patients who received radiotherapy without pelvic involvement, testicular function was normal. Among the remaining 12 patients: –8 were oligospermic or azoospermic–Serum FSH increased threefold–LH increased twofold–Testosterone levels were normal. All nine men who received chemotherapy plus radiotherapy to the abdomen or thigh had decreased testicular size, azoospermia, a fourfold increase in FSH, and a twofold increase in LH levels; testosterone concentration was normal. Recovery was age-related.
6	Shiraishi and Matsuyama 2014[47]	Retrospective, cohort study	mean age of 34.6 years (range, 23–42)	26 (1 sarcoma)	Chemotherapy, including vincristine and cyclophosphamide	Micro TESE in post-chemotherapy azoospermia	The osteosarcoma patient treated with vincristine and cyclophosphamide at age 17 exhibited a Sertoli-cell-only pattern in testicular biopsy with no sperm retrieval.
7	Hsiao et al. 2011[48]	Retrospective, cohort study	mean 34.5 ± 6.6	73 (7 sarcoma)	Various chemotherapy regimens	Spermatozoa retrieval with micro-TESE and fertility rate	Spermatozoa were retrieved in 1/7 patients (14%)

Summary of studies reporting treatment-related effects on spermatogenesis and reproductive outcomes in male patients with sarcoma, including semen parameters, testicular function, and sperm retrieval following chemotherapy and radiotherapy. CDDP = cisplatin; MMC = mitomycin C; VCR = vincristine; ADR = adriamycin (doxorubicin); IFM = ifosfamide; MD-TESE = microdissection testicular sperm extraction; FSH = follicle-stimulating hormone; LH = luteinising hormone.

Table 4: **Gonadal function and reproductive outcomes in male patients with sarcoma cancer.**

azoospermia, and elevated FSH and LH levels, though testosterone remained normal.

These findings underscore the significant gonadotoxicity of sarcoma treatments, particularly platinum-based chemotherapy and radiotherapy, with only partial potential for sperm recovery. Given the low success rates of sperm retrieval in post-treatment azoospermic patients, early fertility preservation strategies, such as sperm cryopreservation, should be prioritised before initiating treatment.

Sarcoma

Female gonadal toxicity

Studies on female sarcoma patients revealed a significant risk of chemotherapy-induced amenorrhea (CIA) and POI, although some retain fertility post-treatment. Female reproductive outcomes and treatment-related ovarian toxicity in sarcoma are summarised in Table 5. Almog et al. reported that ovarian stimulation before chemotherapy resulted in normal oocyte retrieval and fertilisation rates, suggesting effective

No.	Ref	Type of study	Median age	Participants	Intervention	Results
1	Almog et al. 2012[49]	Retrospective, cohort study	31.8	81 (11 sarcoma)	Ovarian hyperstimulation and oocyte retrieval before Chemotherapy (Not specified)	No. of dominant follicles 8.8 ± 5.3, No. of oocytes aspirated 11.93 ± 8.3, Rate of M2 oocytes (%) 80.1 ± 0.16, Fertilization rate (%) 72.2 ± 27.5. Similar to the control cohort.
2	Dicken et al. 2010[56]	Case report	33	1 patient with synovial sarcoma of the vulva	Multimodal treatment including radical hemivulvectomy with bilateral lymph node dissection, brachytherapy with interstitial needles (20 Gy), and external beam radiation therapy (50 Gy)	Natural delivery after radical hemi vulvectomy with bilateral lymph node dissection, brachytherapy with interstitial needles (20 Gy), and external beam radiation therapy (50 Gy).
3	Testolin et al. 1992[53]	Retrospective, cohort study	Not available	11	Radiation therapy with total doses ranging from 50 to 64 Gy	Amenorrhea developed in 1 patient, suggesting a potential impact on ovarian function.
4	Shamberger, Sherins, Ziegler et al. 1981[57]	Retrospective, cohort study	16–43	11	Chemotherapy with doxorubicin, cyclophosphamide, and high doses of methotrexate, with or without radiotherapy	Younger women (16–33 years) who received chemotherapy alone or with radiotherapy to sites distant from the ovaries experienced minimal menstrual irregularities or temporary cessation of menses during therapy; cyclic menses returned promptly after therapy. Gonadotropin and estradiol levels were normal. In contrast, older women (36–43 years) developed persistent amenorrhea with postmenopausal levels of gonadotropins and low estradiol levels. Women who received pelvic radiation plus chemotherapy developed prompt cessation of menses and became functionally castrated.
5	Shamberger, Rosenberg et al. 1981[58]	Retrospective, cohort study	Not available	17 osteosarcomas	Chemotherapy with high-dose methotrexate (HD-MTX), with or without vincristine	The two women who received HD-MTX and all five women who received HD-MTX and VCR had regular cyclic menses not only after therapy but also during treatment. Serum FSH, LH, estradiol, and progesterone levels were normal in all women studied. Among the ten men studied, testicular function was normal in the six patients evaluated initially, several months after the completion of therapy. In contrast, severe oligospermia was noted among four men evaluated during and immediately after treatment.
6	Ghazeeri and Awwad 2012[51]	Case report	26	1	Post chemotherapy (type not specified)	Two successful pregnancies despite chemo-induced premature ovarian failure (Note: The patient's age during treatment was not specified.)
7	Palmert et al. 2004[50]	Case report	Not available	3 osteosarcomas	Ifosfamide-based chemotherapy	All three patients developed premature ovarian failure following chemotherapy.
8	Yang et al. 2021[52]	Retrospective, cohort study	Mean 20.25 (11–45), 41% above 20 years.	122	chemotherapy (type not specified)	Chemotherapy-induced amenorrhea occurred in 46 (36.1%) patients. Among the 62 married patients, 67.8% had given birth after chemotherapy.
9	De Sanctis et al. 2019[54]	Retrospective, cohort study	18	One angiosarcoma patient	Pazopanib treatment	Amenorrhea developed within 2 months of the initiation of pazopanib treatment, and menses returned regularly only after discontinuation of the treatment.
10	Gutkin et al., 2020[55]	Retrospective, cohort study	20	One Ewing sarcoma	Multimodal treatment including irradiation (55.5 Gy) and multi-agent chemotherapy	The patient achieved a natural, successful pregnancy and delivery 12 years after treatment.
11	Hockertz and Velickovic 2018[59]	Case series	18	One Ewing sarcoma	Multimodal treatment including irradiation (55.5 Gy), multi-agent chemotherapy, and sacrectomy	The patient developed a "neosacrum" and achieved a natural, successful pregnancy and delivery 12 years after treatment.
12	Vernaeve et al. 2007[60]	Case series	Mean 21.0 years (95% CI 17.3–24.7) at diagnosis, 33 years in pregnancy attempt	33 (2 sarcoma)	Oocyte donation for fertility in patients treated with chemotherapy or radiotherapy	One sarcoma patient had a single delivery by cesarean section after receiving 55 Gy radiotherapy to the left hemi-pelvis and 10 Gy to the right hemi-pelvis.

Summary of studies reporting treatment-related effects on ovarian function and reproductive outcomes in female patients with sarcoma, including menstrual function, ovarian reserve, and pregnancy outcomes following chemotherapy, radiotherapy, and fertility preservation interventions. CI = confidence interval; FSH = follicle-stimulating hormone; LH = luteinising hormone; VCR = vincristine; HD-MTX = high-dose methotrexate.

Table 5: **Gonadal function and reproductive outcomes in female patients with sarcoma cancer.**

No	Ref	Type of study	Median age	Participant	Treatment	Results
1	Falk et al. 2022[66]	Retrospective, cohort study	36 (M), 35 (F)	36 individuals of fertile age with colorectal cancer (20 males, 16 females)	Oxaliplatin treated CRC individuals of fertile age	FSH and testosterone levels increased in males after chemotherapy treatment but were restored at follow-up. No patients developed hypogonadism. There was a trend towards a decrease in sperm concentration during treatment ($p = 0.063$). And no patients became permanently azoospermic by treatment. No distinct alteration of gonadal function could be observed in females. No statistically significant changes in hormone levels (FSH/LH/Testosterone, SHBG, and Sperm parameters) were observed (compared to the pre-treatment values)
2	Levi et al. 2015[62]	Prospective Observational Study	36 (F), 37 (M)	19 patients with colorectal cancer (11 females aged $\leq$ 43 years, 8 males aged $\leq$ 45 years)	Oxaliplatin treated CRC	In men, FSH and Testosterone levels increased after treatment, and Inhibin-B was slightly reduced post-treatment.
3	Hermann et al. 2005[63]	Retrospective Observational Study	55.2	11 male patients with rectal cancer	Mean cumulative radiation exposure to the testicles was 3.56 Gy (0.7–8.4 Gy).	Mean LH and FSH levels were significantly increased after therapy (350%/185% of the pre-treatment values), and testosterone levels decreased by 78%. No correlation could be found between changes in hormones and doses to the testis.
4	Buchli et al. 2015[64]	Prospective Observational Study	59.9	40 male patients treated for rectal cancer	Radiotherapy and surgery treated rectal cancer male patients	In 1-year follow-up (compared to baseline) -Mean serum and bioavailable Testosterone decreased slightly, while there was a significant increase in mean LH level ($p < 0.001$). The frequency of low serum Testosterone (<8 nmol/L) and elevated LH (>9 IU/L) increased significantly ($p < 0.001$).
5	Bruheim et al. 2008[65]	Retrospective Case-Control Study	66 (45.1–86.0), (Irradiated) or 71 (40.2–94.8), (Nonirradiated)	290 male patients treated for rectal cancer	Adjuvant radiotherapy treated rectal cancer compared to non-adjuvant male patients.	At a median follow-up of 4.7 years post-surgery, serum FSH levels were three times higher in the radiotherapy group than in controls (median: 18.7 vs. 6.3 IU/L, $p < 0.001$). Additionally, 77% of irradiated patients had FSH levels above the reference range (>12 IU/L) compared to 22% in the non-irradiated group ($p < 0.001$). Serum LH levels were 1.7 times higher in irradiated patients (median: 7.5 vs. 4.5 IU/L, $p < 0.001$), and serum testosterone was lower in the irradiated group (mean: 11.1 vs. 13.4 nmol/L, $p < 0.001$), with 27% of irradiated patients having testosterone levels below the reference range (<8 nmol/L) compared to 10% of surgery-only patients ($p < 0.001$).

Summary of studies reporting treatment-related effects on gonadal function and reproductive outcomes in male patients with gastrointestinal cancers, including hormonal changes and semen parameters following chemotherapy, radiotherapy, and surgical interventions. CRC = colorectal cancer; FSH = follicle-stimulating hormone; LH = luteinising hormone; SHBG = sex hormone-binding globulin.

Table 6: **Gonadal function and reproductive outcomes in male patients with GI cancer.**

fertility preservation.[46] However, chemotherapy often leads to ovarian dysfunction, with Yang et al. showing 36.1% of treated patients developing CIA. At the same time, other studies documented POI following ifosfamide-based regimens, though one patient successfully conceived twice despite ovarian failure.[47–49]

Age and treatment intensity influence ovarian outcomes. Younger women (16–33 years) maintained cyclic menses after chemotherapy, whereas older patients (36–43 years) developed persistent amenorrhea with menopausal gonadotropin levels.[45] Pelvic radiotherapy further exacerbates ovarian toxicity, with Testolin et al. reporting amenorrhea in 1 of 11 sarcoma patients, and De Sanctis et al. describing pazopanib-induced amenorrhea, which reversed after treatment cessation.[50,51]

Despite these risks, pregnancy remains possible.[4,52] Gutkin et al. reported natural pregnancies in Ewing sarcoma patients 12 years post-pelvic irradiation (55.5 Gy) and chemotherapy. At the same time, Dicken et al. documented a successful vaginal delivery after extensive vulvar surgery and radiotherapy.[52,53] These findings highlight the need for fertility preservation strategies in young sarcoma patients, particularly those undergoing high-dose chemotherapy or pelvic irradiation. While ovarian failure is common, some women regain menstrual function, and spontaneous or assisted pregnancies remain viable options for survivors.

Colorectal cancer

Male gonadal toxicity

Studies evaluating gonadal toxicity in male colorectal patients with cancer indicated that chemotherapy and radiotherapy have important effects on hormonal levels and sperm function. However, long-term recovery is possible in some cases. Evidence regarding male gonadal function and hormonal changes in gastrointestinal malignancies is detailed in Table 6. Falk et al. reported that FSH and testosterone levels increased during chemotherapy but normalised at follow-up, with

No	Ref	Type of study	Median age	Participant	Treatment	Results
1	Sahin et al. 2019[67]	Retrospective, cohort study	40	60 premenopausal female patients under 50 years with stages I-III colon cancer	Adjuvant chemotherapy: 5-Fluorouracil (5-FU) alone (n = 22), 5-FU + oxaliplatin (n = 27)	Persistence Amenorrhea: 20% for all groups 5-FU alone- 18% 5-FU + oxaliplatin 22% Age < 44 (n = 28)- 3.5% 5-FU + oxaliplatin- 6% 5-FU- 0 Age ≥ 44 (n = 21)- 42.8% 5-FU + oxaliplatin- 45% 5-FU- 0–40% Age of 44 years and older (hazard ratio: 29.3; 95% confidence interval: 2.8–309.2, p = 0.005) and menarche age of 14 years and older (hazard ratio: 7.6; 95% confidence interval: 1.2–49, p = 0.076) were significantly associated with increased risk of persistent amenorrhea.
2	Wan et al. 2015[68]	Retrospective, cohort study	35.1	123 premenopausal women aged ≤ 40 years with colorectal cancer (CRC)	Adjuvant chemotherapy and chemoradiotherapy. Colon cancer (n = 72): FOLFOX (5-FU, leucovorin, oxaliplatin), XELOX (capecitabine, oxaliplatin). Rectal cancer (n = 51): chemoradiotherapy	Incidence of long-term amenorrhea- Colon cancer: 4.2%. Rectal cancer: 94.1%. No significant difference in amenorrhea incidence between FOLFOX and XELOX regimens (4.9% vs. 5.6%; p = 0.913).
3	Cercek et al. 2013[69]	Retrospective, cohort study	33.5	49 women aged ≤ 50 years with stage II or III colorectal cancer	Adjuvant FOLFOX chemotherapy	In total, 41% (n = 20) experienced amenorrhea during chemotherapy. 16% had persistent amenorrhea 1 year after completion of chemotherapy. Younger than 40 (n = 32)–13%. 40 and older 40 (n = 17)–24%. Not statistically significantly higher in women older than 40 (24% vs. 13%; p ¼ 0.423). 36%. 36% of the patients reported attempted pregnancy, and 44% had children after treatment.
4	Letourneau et al. 2012[72]	Retrospective, cohort study	34.1	50 female gastrointestinal cancer patients	Chemotherapy (regimens not specified)	Acute ovarian failure at 12 months: 23%. Probability of early menopause despite menses: 80% at age 20, 50% at age 35 (p < 0.001). Acute ovarian failure increased with age: 0% at age 30, 40% at age 40.
5	Falk et al. 2022[61]	Retrospective, cohort study	36 (M), 35 (F)	36 patients (20 males, 16 females) with CRC	Oxaliplatin-based chemotherapy	No distinct alteration of gonadal function could be observed in females. No statistically significant difference in hormone levels (compared to the pre-treatment values)
6	Levi et al. 2015[62]	Prospective study	36 (F), 37 (M)	19 patients (11 females, 8 males) with CRC	Oxaliplatin treated CRC	AMH decreased post-treatment, but remained above the detection limit in 9/11 patients (p < 0.05). In 80% female patients, AMH and FSH did not exceed the premenopausal range. All maintained menses or resumed menses post-treatment.
7	Holloman et al. 2017[70]	Case report	40	1 female patient with pancreatic cancer	Whipple procedure and chemoradiation with gemcitabine	Despite a history of anovulatory infertility and Polycystic Ovary Syndrome (PCOS), the patient achieved a full-term spontaneous pregnancy without fertility treatment following cancer therapy.
8	Segelman et al. 2019[71]	Prospective study	71 RT-group 61.5 RT + group	125	Women treated for rectal cancer with or without pelvic radiotherapy	98 women who received preoperative chemoradiation + surgery and 27 women who had surgery alone, assessing serum androgen levels before treatment and ~1 year after. The RT group showed a significant decline in ovarian androgen levels, while no such change occurred in the surgery-only group. Free testosterone showed a similar decrease (9.1–7.9 pmol/L, p < 0.001), and these declines were accompanied by induction of amenorrhea in the women who received RT (consistent with ovarian failure).

Summary of studies reporting treatment-related effects on ovarian function and reproductive outcomes in female patients with gastrointestinal cancers, including menstrual outcomes, ovarian reserve, and pregnancy following chemotherapy, radiotherapy, and combined treatment approaches. CRC = colorectal cancer; FSH = follicle-stimulating hormone; AMH = anti-Müllerian hormone; RT = radiotherapy.

***Table 7*: Gonadal function and reproductive outcomes in female patients with GI cancer.**

No	Ref	Type of study	Median age	Participant	Treatment	Results
1	Aasebø et al. 1991[73]	Retrospective Study	60–64	62 (12 received chemotherapy)	NSCLC: Cisplatin (70 mg/m^2 IV) + Etoposide (100 mg/m^2 IV on day 1, 200 mg/m^2 orally on days 2 and 3) every 3 weeks for 3–4 cycles SCLC: VAC regimen (Vincristine 2 mg IV, Doxorubicin 50 mg/m^2 IV, Cyclophosphamide 1000 mg/m^2 IV) every 3 weeks for 5 cycles.	Baseline testosterone was lower in lung cancer patients compared to COPD controls. In non-responders, testosterone, FSH, and LH decreased during treatment and remained low post-treatment. In responders, testosterone recovered to normal within 12 weeks, and SHBG declined significantly post-treatment.
2	Aasebø et al. 1989[74]	Retrospective Study	63	12	Cisplatin (70 mg/m^2) + Etoposide (100 mg/m^2 IV day 1, 200 mg/m^2 PO days 2–3) every 3 weeks for 3–4 cycles	Testosterone levels remained normal and unchanged during the 9-week chemotherapy period. SHBG levels significantly increased, FSH increased above normal range, and LH rose slightly (within normal limits). The study concluded that cyclic chemotherapy can induce temporary endocrine gonadal dysfunction in men, even if testosterone remains stable.

Summary of studies reporting treatment-related effects on gonadal function in male patients with lung cancer, including hormonal changes following chemotherapy. NSCLC = non-small-cell lung cancer; SCLC = small-cell lung cancer; VAC = vincristine, doxorubicin, and cyclophosphamide; FSH = follicle-stimulating hormone; LH = luteinising hormone; SHBG = sex hormone-binding globulin.

Table 8: **Gonadal function and reproductive outcomes in male patients with lung cancer.**

no cases of permanent azoospermia.[54] Similarly, Levi et al. found that FSH and testosterone levels increased post-treatment, with a slight reduction in Inhibin-B, suggesting transient gonadal dysfunction without permanent impairment.[55]

Radiotherapy had a more pronounced and persistent impact on gonadal function. Hermann et al. found that testicular radiation exposure (mean 3.56 Gy) led to a 350% increase in LH and a 185% increase in FSH. At the same time, testosterone levels declined to 78% of baseline values, with no clear correlation between hormone changes and radiation dose.[56] Buchli et al. further reported that low testosterone levels (<8 nmol/L) and elevated LH (>9 IU/L) were significantly more frequent post-radiotherapy, suggesting long-term disruption of testicular function.[57] Bruheim et al. reported consistent findings: FSH levels were three times higher in irradiated patients than in controls (18.7 vs. 6.3 IU/L, $p < 0.001$), and 77% of irradiated patients had FSH levels exceeding the reference range. Additionally, serum testosterone levels were significantly lower in irradiated patients (11.1 vs. 13.4 nmol/L, $p < 0.001$), with 27% falling below the reference range compared to 10% of non-irradiated patients.[58]

Colorectal cancer

Female gonadal toxicity

Studies on chemotherapy-induced ovarian dysfunction in premenopausal women with colorectal and gastrointestinal cancers indicate varying risks of amenorrhea and POI, although some retain fertility post-treatment. Female gonadal function and reproductive outcomes in gastrointestinal malignancies are summarised in Table 7. Persistent amenorrhea was reported in 20% of patients with colorectal cancer treated with adjuvant chemotherapy, with a significantly higher risk observed in women aged $\geq$ 44 years (42.8%) compared to younger patients (3.5%).[59] Similarly, Wan et al. reported that chemotherapy-induced amenorrhea was rare in colon patients with cancer (4.2%) but significantly higher in rectal patients with cancer (94.1%), likely due to pelvic radiation effects.[60]

The impact of chemotherapy on ovarian function appears age-dependent. Among women receiving FOLFOX chemotherapy (fluoropyrimidine and oxaliplatin), 41% developed amenorrhea during treatment, and 16% experienced persistent amenorrhea one year later, with a slightly higher risk observed in older patients.[61]

Despite these risks, some treatments appear to have a lesser impact on ovarian function. Falk et al. conducted a retrospective study, analysing post-treatment patient data to assess gonadal function in women treated with oxaliplatin, and found no significant changes.[54] Levi et al. conducted a prospective study evaluating ovarian reserve markers, including AMH, in young women undergoing chemotherapy for gastrointestinal cancers. Although they reported reductions in AMH levels following treatment, most patients resumed menses.[55]

Pregnancy remains feasible after treatment.[4,52] Cercek et al. found that 36% of patients in a retrospective cohort attempted pregnancy, and 44% successfully conceived post-treatment.[61] Similarly, a patient with a history of pancreatic cancer, Whipple procedure, and chemoradiation, conceived naturally and delivered a full-term infant despite prior anovulatory infertility.[62]

Fertility outcomes for young women receiving pelvic radiation as part of rectal cancer treatment showed high rates of therapy-induced amenorrhea. In a retrospective cohort study, Wan et al. show long-term amenorrhea occurred in 94.1% of rectal patients with cancer who received chemoradiotherapy, compared to only 4.2% in colon patients with cancer treated with chemotherapy alone.[60] The prospective study of Segelman et al. found that women receiving pelvic radiotherapy for rectal

No.	Ref	Type of study	Median age	Participant	Treatment	Results
1	Mawet et al. 2023[76]	Case Report	38	1	Lorlatinib	A 38-year-old woman with ROS1-positive non-small cell lung cancer (NSCLC) was treated with lorlatinib as second-line therapy. She became pregnant while on treatment, with an estimated embryo exposure to the drug of about four weeks. The pregnancy was terminated at 21 + 4 weeks of gestation. The fetus, weighing 539 g, showed no malformations upon conventional examination, and there were no maternal complications.
2	Shen et al. 2021[77]	Retrospective Study	29.4	N = 30, pregnancies = 34	Sirolimus treatment in 17/34 pregnancies	This study analysed 34 pregnancies among 30 women diagnosed with lymphangioleiomyomatosis (LAM). Seventeen pregnancies involved sirolimus treatment. Patients taking sirolimus before pregnancy had a higher risk of spontaneous abortion (5 out of 6 cases, or 83.3%). Discontinuation of sirolimus before or during pregnancy did not increase adverse neonatal outcomes.
3	Merideth et al. 2020[78]	Retrospective Study	31	64 participants, 15 were survivors of pleuropulmonary blastoma	Surgery, Chemotherapy, and radiation	Among 64 female DICER1 mutation carriers, 15 (23.4%) were survivors of pleuropulmonary blastoma. The study found that reproductive outcomes, including pubertal development, menarche, and menopause, occurred at ages similar to the general population. Fertility was generally preserved despite lower-than-expected anti-Müllerian hormone levels. All women who attempted conception successfully delivered liveborn children, and the miscarriage rate was comparable to that of the general population.
4	Cathcart-Rake et al. 2019[79]	Retrospective Study	44	182	Chemotherapy (including platinum-based regimens) and Targeted Therapy	Among 182 women with lung cancer, 85 (46.7%) received chemotherapy within one year of diagnosis, and 26 (15.9%) received targeted therapy in combination with chemotherapy. Of those who received chemotherapy, 64% reported becoming menopausal within one year of diagnosis, compared to 15% who did not receive systemic therapy. Platinum-based chemotherapy regimens were commonly associated with high rates of menopause.
5	Cathcart-Rake et al. 2019[80]	Retrospective Study	37–44	328	Not specified; focus on pregnancy experiences and outcomes in LAM patients.	The study examined pregnancy outcomes among women diagnosed with LAM before, during, or after pregnancy. Full-term births were more common in women diagnosed after pregnancy. In contrast, premature births and miscarriages were more frequent in women diagnosed during pregnancy. Pregnancy terminations were more common in women diagnosed with LAM during pregnancy due to concerns about maternal health.
6	Grillo 1971[81]	Case Report	25	1	left lower lobectomy	A 25-year-old woman underwent a left lower lobectomy. Postoperatively, her human chorionic gonadotropin (HCG) levels were elevated and then returned to normal, only to rise again during a successful pregnancy a few months later.

Summary of studies reporting treatment-related effects on reproductive outcomes in female patients with lung cancer, including menstrual function, menopause, and pregnancy outcomes following chemotherapy, targeted therapy, and surgical interventions. NSCLC = non-small-cell lung cancer; LAM = lymphangioleiomyomatosis; HCG = human chorionic gonadotropin.

Table 9: **Gonadal function and reproductive outcomes in female patients with lung cancer.**

cancer experienced a significant decline in ovarian androgen levels and increased rates of amenorrhea, indicating POI. In contrast, women who had surgery without radiation showed no hormonal changes, underscoring the gonadotoxicity of pelvic RT.[63]

Lung cancer

Male gonadal toxicity

Studies investigating the impact of chemotherapy on gonadal function in male lung patients with cancer suggested significant endocrine disruptions, particularly in testosterone, FSH, and LH levels, depending on treatment response. Male reproductive and endocrine outcomes in lung malignancies are summarised in Table 8. Aasebø et al. examined cisplatin-etoposide and VAC regimens in patients with lung cancer. They found that baseline testosterone levels were significantly lower in patients with cancer compared to those with chronic obstructive pulmonary disease (COPD). During chemotherapy, testosterone levels further declined in non-responders but remained stable in responders. Non-responders continued to exhibit low testosterone levels 12 weeks post-treatment, whereas responders regained normal levels.[64]

In addition to testosterone, chemotherapy influenced gonadotropins and sex hormone-binding globulin (SHBG). FSH and LH levels declined in non-responders but remained stable in responders, while SHBG levels significantly decreased post-chemotherapy in those who responded to treatment. Aasebø et al. (1989) further confirmed that cisplatin-etoposide chemotherapy increased SHBG and FSH levels, while LH remained within the normal range. The findings indicate that cyclic chemotherapy induces endocrine dysfunction, with a greater impact on hormone regulation in patients who do not respond to treatment.[65]

Lung cancer

Female gonadal toxicity

Studies examining reproductive outcomes in women with lung cancer and pulmonary diseases highlighted variable fertility and pregnancy outcomes depending on treatment type and timing.[66] Gonadal toxicity and reproductive outcomes in women with lung malignancies are summarised in Table 9. Mawet et al. reported a case of a 38-year-old woman with ROS1-positive non-small cell lung cancer (NSCLC) who became pregnant while on Lorlatinib therapy. The pregnancy was terminated at 21 + 4 weeks, and the fetus showed no malformations.[67]

Sirolimus therapy was associated with a high risk of spontaneous abortion. Shen et al. found that among 34 pregnancies in sirolimus-treated patients, spontaneous abortion occurred in 83.3% of cases where sirolimus was taken before pregnancy. In contrast, patients who discontinued the drug before or during pregnancy had no increase in neonatal complications.[68]

Survivors of pleuropulmonary blastoma (PPB) generally retained fertility. Merideth et al. found that all women who carried a DICER1 mutation and attempted conception delivered liveborn children, and that pubertal development, menarche, and menopause occurred at normal ages, despite lower-than-expected AMH levels.[69]

Chemotherapy has a significant impact on ovarian function. Cathcart-Rake et al. found that among lung patients with cancer, 64% of those who received chemotherapy became menopausal within a year, compared to 15% of those who did not receive systemic therapy. Platinum-based chemotherapy regimens were most associated with early menopause, with a mean age of menopause onset at 46 years.[70]

Pregnancy outcomes in patients with lymphangioleiomyomatosis (LAM) varied based on diagnosis timing. Cohen et al. found that full-term births were more common in women diagnosed after pregnancy. In contrast, premature births and miscarriages were more frequent in women diagnosed during pregnancy, often leading to pregnancy terminations due to maternal health concerns.[71]

Fertility preservation and subfertility outcomes

Supplementary data highlighted fertility preservation outcomes (Supplementary Tables S1–S10). In melanoma, Luke et al. found that women undergoing ART using autologous oocytes had a 53.5% live birth rate, with adjusted odds of live birth comparable to non-cancer controls.[72]

In sarcoma, male fertility preservation via sperm cryopreservation and electroejaculation showed variable post-thaw motility and counts,[73,74] with mixed success in achieving pregnancies.[75,76] Meistrich et al. reported that lower cyclophosphamide doses (<7.5 g/m^2) were associated with better spermatogenic recovery.[16] In patients with female sarcoma, ovarian stimulation before treatment yielded satisfactory outcomes, with oocyte numbers and maturation rates similar to controls.[46,77,78] Successful pregnancies following ovarian tissue transplantation were reported.[79,80] Survivorship studies revealed high unmet needs in fertility counselling, with infertility reported in 21% of males and 46% of females.[81]

In gastrointestinal cancers, both male and female patients exhibited preserved fertility parameters before treatment.[82,83] Female patients showed comparable oocyte retrieval and fertilisation rates to non-cancer controls.[46,84] Notably, CRC survivors had a lower total fertility rate in women, but not in men.[85] Fertility preservation services were rarely utilised among lung patients with cancer, with only 2% receiving counselling.[86]

Laparoscopic ovarian transposition before pelvic radiotherapy preserved ovarian function in 50–90% of cases across tumour types.[87–89] Several cases reported spontaneous pregnancies or successful IVF following transposition,[90–92] Though the risk of POI remained.[93]

Uterine transposition, although infrequently utilised, was associated with functional uterine preservation and successful pregnancies in selected cases.[15,94] However, complications such as cervical ischemia and uterine necrosis were observed, indicating that while promising, the technique requires careful patient selection and surgical expertise.

Discussion

The impact of anticancer treatments on reproductive outcomes is a key issue for young patients with cancer.[95] While fertility represents the main outcome affected by treatment-related gonadal toxicity, other hormone-related outcomes are potentially altered by gonadal impairment and may affect different systems, such as cardiovascular, cognitive, and neurological. Although there is robust evidence regarding treatment-related reproductive toxicity in patients with breast cancer,[96] Data regarding these other tumour types are minimal and lack high-quality evidence. Most studies are retrospective in nature and include heterogeneous populations, small sample sizes, and limited follow-up. Moreover, considerable variability in treatment regimens and endpoints complicates the attribution of gonadotoxic effects to specific interventions.

Exploratory meta-analyses conducted in this study further illustrate these limitations. Although statistical pooling was technically feasible, the resulting estimates were imprecise and largely driven by substantial clinical heterogeneity across studies, including differences in treatment regimens, exposure to pelvic radiotherapy, and duration of follow-up.

Our findings identify key trends in gonadal toxicity and fertility outcomes that can inform clinical decision-making and highlight priorities for future research.

In men with melanoma, current data indicate a mild gonadotoxic profile of immune checkpoint inhibitors (ICIs). Most patients maintain normal semen parameters, though rare cases of orchitis and azoospermia have been reported.[28,29,34] Long-term fertility appears largely preserved, with population studies showing no difference in post-cancer paternity rates.[33] In women, population-based studies likewise show no significant increase in POI or infertility risk compared to controls,[35,36] And many survivors achieve pregnancies. Overall, melanoma treatments appear to carry a low gonadotoxic burden, though the impact of newer regimens requires further study. Evidence regarding immunotherapy and targeted therapies is largely derived from case reports and small series and should therefore be considered highly limited and inconclusive, with no putative underlying mechanism. Preliminary biomarker evidence from a prospective clinical trial analysis has suggested a decline in AMH levels among young women receiving immune checkpoint inhibition for melanoma, raising the possibility of subclinical ovarian reserve impairment.[39,40] Despite the relatively low gonadotoxic profile of immune checkpoint inhibitors, fertility counselling and preservation discussion should be offered to young patients before treatment initiation due to uncertainty regarding long-term reproductive effects and potential combination therapy exposure.

In men with Sarcoma, chemotherapy regimens with alkylating agents and platinum compounds cause high rates of azoospermia or oligospermia, often long-term, with recovery influenced by dose and age.[42] In women, ifosfamide-based protocols carry a substantial risk of amenorrhea and POI, again with age as a key determinant.[49] Proactive fertility preservation is strongly indicated in sarcoma patients of reproductive age. The transient amenorrhea observed with pazopanib may reflect reversible inhibition of follicular growth through disruption of ovarian angiogenesis and growth factor signalling pathways rather than depletion of the primordial follicle pool, consistent with the established role of VEGF-mediated vascularisation in follicle maturation and the reversible ovarian effects described with anti-angiogenic and targeted therapies.[8,97]

In men with Colorectal cancer, oxaliplatin-based chemotherapy may cause transient hormonal changes, usually reversible, while pelvic radiation remains highly gonadotoxic unless testes are shielded. Fertility rates are not reduced in large cohorts.[38,54] In women, younger patients often resume menses after chemotherapy, while those >40 years have high rates of persistent amenorrhea.[61,98] The addition of pelvic radiotherapy for rectal cancer dramatically increases risk, with nearly universal ovarian failure unless ovaries are transposed.[60,63] Overall, chemotherapy alone carries a moderate risk, whereas radiation exposure represents the most deleterious treatment-related factor for long-term ovarian function.

In men with lung cancer, suppressed testosterone and altered gonadotropins are reported during chemotherapy, with poorer recovery in non-responders.[64] Data on sperm parameters are scarce, and fertility preservation is rarely offered despite improved survival. In women, platinum-based chemotherapy poses a high risk of premature menopause, with rates up to 64% within one year.[70] Fertility counselling and preservation remain markedly underutilised.[23] Data on targeted therapies in pregnancy are sparse and conflicting.[67,68]

Fig. 2 summarises the gonadotoxicity risk associated with various anticancer treatments. Age and treatment type represent key factors determining the risk for treatment-related gonadal toxicity, especially in women. Alkylating agents and platinum-based regimens show the highest gonadotoxicity in both sexes,[8,16] due to enhanced follicular burnout or via other gonadotoxic mechanisms. Sarcoma regimens involving high-dose alkylates are particularly harmful, while colorectal regimens like FOLFOX, which are less gonadotoxic, carry a lower risk.[54,55] Immunotherapy and targeted agents appear safer, though long-term data are limited.[11,22]

Emerging evidence suggests that immune checkpoint inhibitors may influence ovarian reserve. A prospective biomarker study reported a decline in anti-Müllerian hormone (AMH) levels in young women treated with ipilimumab, raising concern for potential subclinical effects on ovarian reserve. In addition, pharmacovigilance analyses have described immune-related reproductive endocrine events affecting both male and female gonadal function. Although the clinical significance of these findings remains uncertain, they support continued monitoring of reproductive outcomes in patients receiving immune checkpoint inhibitors.[39,99]

The timing of gonadal recovery varies considerably across treatments: while many women resume menses within a year after chemotherapy, failure to resume menses within two years suggests irreversible POI.[4,61] Men can experience a gradual recovery of spermatogenesis over 1–2 years post-treatment if spermatogonial stem cells survive.

Pelvic radiotherapy is the most harmful treatment to ovarian function. When ovaries are within the radiation field, ovarian failure rates can exceed 90%.[68,71] Ovarian transposition remains the best method to protect the ovaries from radiation-related injury, though scatter may occur in about 10% of cases.[97] In men, scattered radiation from pelvic fields reduces sperm counts and testosterone levels, consistent with Sertoli and Leydig cell damage.[65] The impact of radiation on the uterus and potential subsequent fibrosis is unclear, whereas former evidence regarding radiation effects relies on studies in survivors of childhood cancers, in which

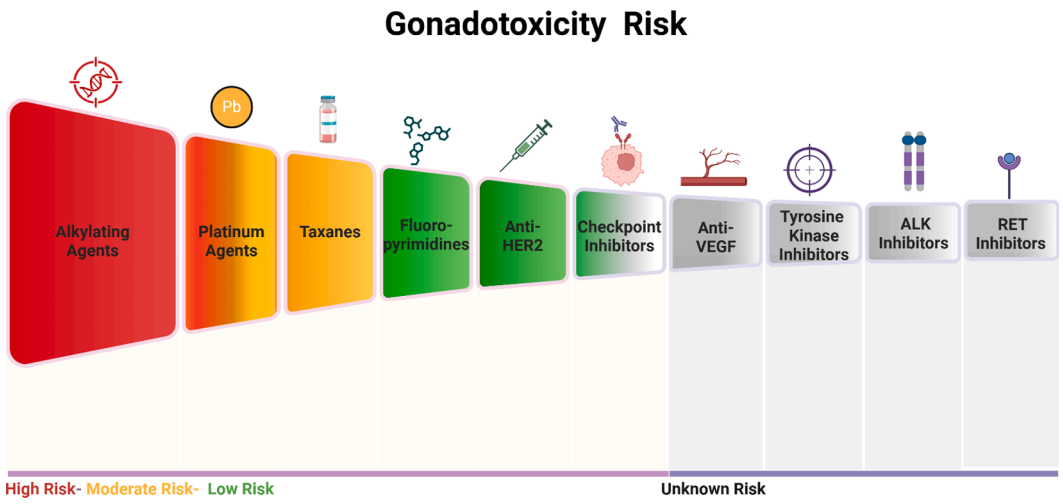

***Fig. 2:* Gonadotoxicity risk by cancer treatment class.** Relative gonadotoxicity risk across systemic anticancer therapies, illustrating high risk with alkylating and platinum agents, intermediate risk with taxanes, lower risk with fluoropyrimidines and anti-HER2 therapies, and uncertain risk with targeted and immune-based treatments. Abbreviations: HER2, human epidermal growth factor receptor 2; VEGF, vascular endothelial growth factor; ALK, anaplastic lymphoma kinase; RET, rearranged during transfection.

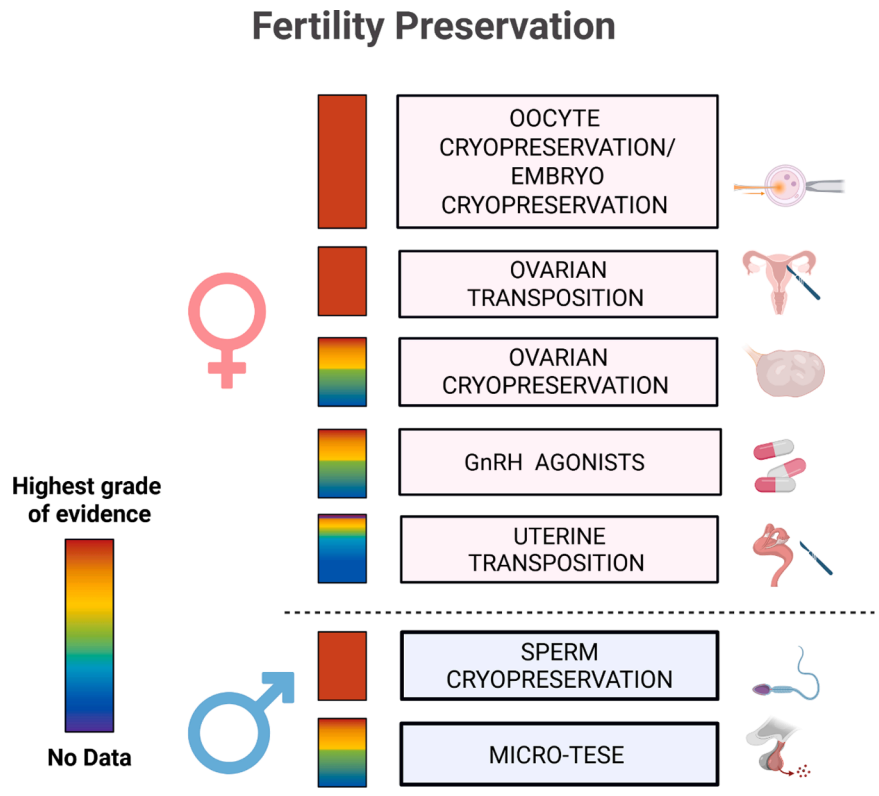

***Fig. 3:* Fertility preservation strategies, graded evidence summary for male and female interventions.** Fertility preservation options in oncology, demonstrating established and emerging strategies for females and males, with colour-coding indicating the strength of clinical evidence. Colour scale represents strength of evidence, ranging from highest grade of evidence to no available data. Abbreviations: GnRH, gonadotropin-releasing hormone; micro-TESE, microsurgical testicular sperm extraction.

treatment fields and radiotherapy modality greatly differ from current regimens for rectal cancer.[103] One study conducted in a small cohort of rectal or anal patients with cancer indicated a significant impairment of uterine perfusion on MRI. Still, the correlation to future reproductive outcome was not shown.[104]

With growing numbers of young patients with cancer and improved survival due to newer treatments, the need to address fertility outcomes and timely referral for fertility preservation remains unmet. It had been shown that among lung and gastrointestinal patients with cancer, the rate of referral for fertility preservation had been low, presumably due to assumptions about prognosis. 24 Studies show patients value fertility discussions and regret missed opportunities, 7 emphasising the need to integrate fertility preservation into standard oncological care for young patients with cancer candidates to a curative intent, regardless of cancer type.

Collectively, the available evidence suggests that fertility risk in these malignancies is largely treatment-dependent rather than disease-specific. Across studies, radiation exposure and the use of highly gonadotoxic chemotherapy regimens, particularly alkylating agents and platinum-based therapies, have been studied.

Given the above patterns of gonadotoxicity, fertility preservation is mandatory in interested patients across all cancer types. Current ESMO guidelines and recent ASCO guideline update (2025) reinforce the importance of offering these approaches, emphasising the need for early, proactive intervention,[4] as elaborated in Fig. 3.

Sperm Cryopreservation: Sperm banking remains the cornerstone FP strategy for males and should be offered to all pubertal patients before starting systemic anticancer therapy. The procedure is fast, low-risk, and has excellent success rates for future assisted reproduction. In cases of post-treatment azoospermia, microsurgical testicular sperm extraction (TESE) offers a secondary option, with some sarcoma patients achieving pregnancies through this method.[100]

Oocyte and Embryo Cryopreservation: For females, controlled ovarian stimulation with egg or embryo freezing is the standard FP method and is feasible even with limited time before treatment. Studies have shown that ovarian responsiveness in patients with cancer is comparable to that of healthy controls.[46] Embryo cryopreservation has resulted

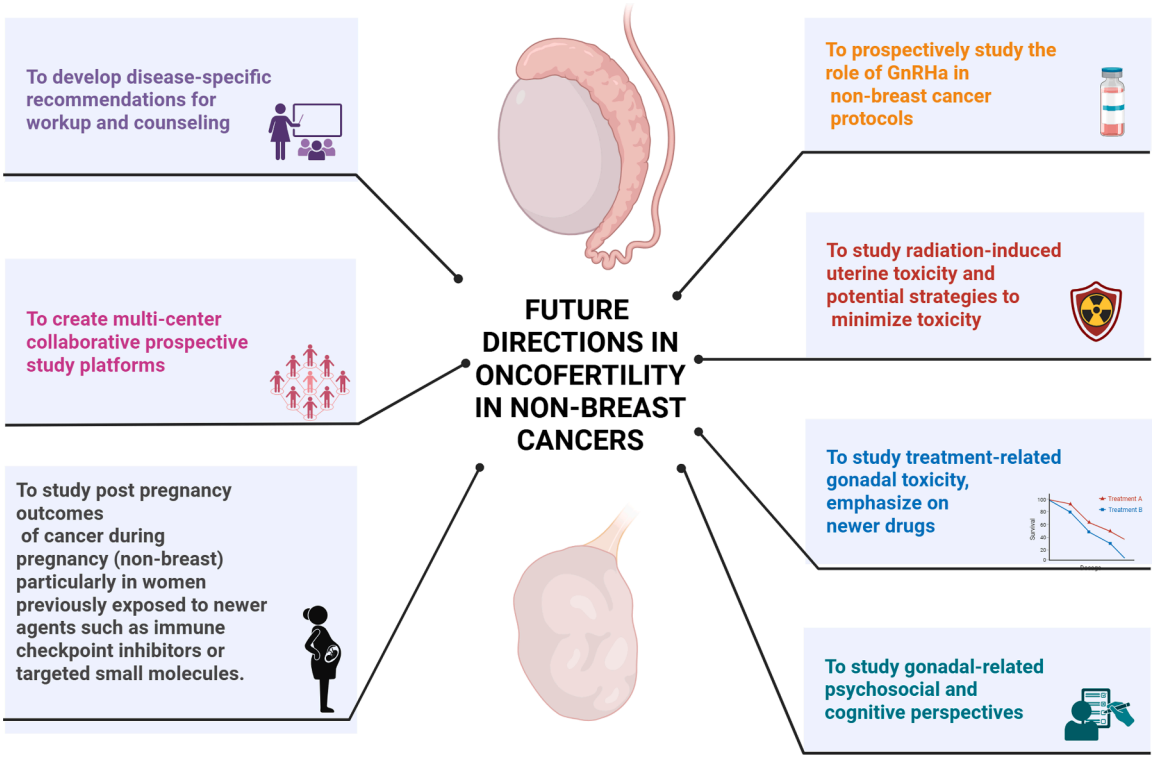

Fig. 4: **Oncofertility care in patients with cancer other than breast malignancies.** Key future research priorities in oncofertility for non-breast malignancies, including prospective studies on treatment-related gonadotoxicity, fertility preservation strategies, pregnancy outcomes after novel therapies, uterine radiation toxicity, and psychosocial reproductive health. Abbreviations: GnRHa, gonadotropin-releasing hormone agonists.

in successful post-treatment pregnancies, as demonstrated in cases of colorectal cancer.[101]

Ovarian tissue cryopreservation (OTC) provides a fertility preservation option for patients who cannot postpone anticancer treatment long enough (2–3 weeks) to undergo ovarian stimulation for oocyte or embryo cryopreservation, or for prepubertal girls. In all other cases, oocyte or embryo cryopreservation should remain the preferred approach. Nonetheless, OTC is no longer considered investigational, and its use is expanding, with successful births reported in patients with solid tumours.[21]

GnRHa Co-Treatment: Use of GnRHa during chemotherapy has shown benefit in preserving ovarian function, mainly in breast cancer.[24] However, clinical practice guidelines note that it should not replace established FP techniques.[4] Data on the effect of GnRHa in the setting of non-breast, non-haematological patients with cancer are lacking and warrant further study.

Surgical Approaches: Ovarian transposition (oophoropexy) before pelvic radiation can preserve ovarian function in 85–90% of cases and is considered a standard recommendation before pelvic irradiation.[87] Nevertheless, uterine transposition, which has recently arisen as an option to ameliorate the effect of radiation on the uterus, should be further studied in terms of risk and benefit. Therefore, it should be considered in selected cases under specific study protocols.

Cost-effectiveness and procedural safety of fertility preservation strategies remain underexplored in non-breast solid malignancies. Incorporating standardised economic and safety evaluations into prospective oncofertility studies will be important for informing equitable access and optimising resource allocation.

As cancer treatment evolves, targeted therapies (such as ALK and EGFR inhibitors in lung cancer and BRAF and MEK inhibitors in melanoma) are increasingly used in younger patients, yet their long-term effects on fertility remain largely unknown. Systematic data collection is needed to determine whether prolonged exposure to these agents contributes to infertility. Early signals, such as those observed with sirolimus in lymphangioleiomyomatosis, suggest that some targeted therapies may adversely affect reproductive outcomes; however, larger controlled studies are required.[102]

Future research directions, outlined in Fig. 4, should include large, multi-institutional prospective cohorts that track markers of gonadal function and fertility outcomes in young patients across these cancers, from diagnosis through survivorship. The inclusion of biobanking (for hormonal and genetic studies) and patient-reported quality of life related to fertility will help correlate clinical and personal impacts. In parallel, clinical trials or registries evaluating fertility-preservation interventions could provide evidence to refine guidelines for these malignancies. Collaboration between oncologists, reproductive specialists, and researchers will be essential to advance these goals.

This systematic review aimed to synthesise the available evidence on oncofertility outcomes in non-breast solid malignancies that are increasingly diagnosed in young adults, a population for which high-quality fertility data remain limited compared with breast and hematologic cancers. The evidence base was characterised by substantial methodological heterogeneity, including retrospective designs, small institutional cohorts, registry-based analyses, and case reports, with relatively few prospective longitudinal studies. The limited reporting of sex-specific outcomes in some studies represents an additional limitation.

The predominance of studies originating from high-income countries may also limit the generalizability of fertility risk estimates across diverse healthcare systems and resource settings.

Considerable variability was observed in outcome definitions and measurement approaches. Some studies focused on surrogate hormonal markers (e.g., AMH, inhibin-B), whereas others reported clinically meaningful reproductive outcomes, including amenorrhea, azoospermia, pregnancy, or live birth. Inconsistent definitions of ovarian failure and recovery further limited comparability across studies and have been recognised as a major barrier to evidence synthesis in oncofertility research (Rodriguez-Wallberg et al., 2023).

Although eligibility was restricted to adult populations (≥18 years), substantial variation in age distribution within cohorts likely contributed to differences in gonadal outcomes, given the strong age dependence of ovarian reserve and spermatogenic recovery. Additional sources of heterogeneity included differences in treatment exposure, particularly the inclusion of pelvic radiotherapy cohorts alongside chemotherapy-only populations, variability in follow-up duration, and inconsistent reporting of fertility recovery timelines.

Finally, the inclusion of case reports and case series, while valuable for identifying rare reproductive toxicities, limits the ability to estimate treatment-specific risks and may introduce publication bias. Formal assessment of publication bias was not performed due to the limited number of studies per outcome; however, the inclusion of case reports and small studies may increase the risk of selective reporting.

Taken together, these limitations highlight the need for prospective, multi-institutional studies with standardised reporting of reproductive endpoints, uniform definitions of gonadal recovery, and longer follow-up better to characterise fertility outcomes in survivors of non-breast solid malignancies.

Contributors

NS, IBA, and ML conceived the study. NS, AB, and IW developed the methodology. NS performed the formal analysis and curated the data. NS, IBA, and ML drafted the original manuscript. IBA and ML supervised the study. JB contributed to study selection and data extraction. All authors contributed to data interpretation, critically revised the manuscript, and approved the final version. NS and AB accessed and verified the underlying data.

Data sharing statement

This study is a systematic review of previously published data. No individual participant data were generated. All data analyses in this study are available in the published articles included in the review. Statistical code used for the exploratory meta-analyses is available from the corresponding author upon reasonable request.

Declaration of interests

ML reports grants to his institution from Gilead; consulting fees from Roche, Lilly, Novartis, AstraZeneca, Pfizer, Seagen, Gilead, MSD, Exact Sciences, Pierre Fabre, Menarini, and Nordic Pharma; honoraria from Roche, Lilly, Novartis, Pfizer, AstraZeneca, Takeda, Ipsen, Sandoz, Libbs, Daiichi Sankyo, Gilead, and Menarini; and travel support from Gilead, Daiichi Sankyo, and Roche.

IBA reports grants from ICRF and ISF; and honoraria from AstraZeneca, Merck, MSD, and Bristol Myers Squibb.

AB reports honoraria from MSD, Bristol Myers Squibb, Pierre Fabre, and Immunocore.

IW reports internal institutional support from Rambam Health Care Campus.

All other authors declare no competing interests.

Acknowledgements

This research received internal support from the the Fishman Oncology Center, Rambam Health Care Campus, Israel. No specific grant funding was received for this work. We thank the Technion library staff for assistance with literature retrieval and technical support during the review process. The authors used ChatGPT (OpenAI) to assist with language editing. The authors take full responsibility for the content of the manuscript. Figures were created with BioRender.com.

Additional supporting references are provided in the Supplementary Appendix[103–127]

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2026.103979.

References

1 Zhao J, Xu L, Sun J, et al. Global trends in incidence, death, burden and risk factors of early-onset cancer from 1990 to 2019. *BMJ Oncol*. 2023;2(1):e000049. https://doi.org/10.1136/bmjonc-2023-000049.
2 Sung H, Jiang C, Bandi P, et al. Differences in cancer rates among adults born between 1920 and 1990 in the USA: an analysis of population-based cancer registry data. *Lancet Public Health*. 2024;9(8):e583–e593. https://doi.org/10.1016/S2468-2667(24)00156-7.
3 Rosenberg SM, Partridge AH. Premature menopause in young breast cancer: effects on quality of life and treatment interventions. *J Thorac Dis*. 2013;5 Suppl 1(Suppl 1):S55–S61. https://doi.org/10.3978/j.issn.2072-1439.2013.06.20.
4 Lambertini M, Peccatori FA, Demeestere I, et al. Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO clinical practice guidelines†. *Ann Oncol*. 2020;31(12):1664–1678. https://doi.org/10.1016/j.annonc.2020.09.006.
5 Ganz PA, Greendale GA, Petersen L, Kahn B, Bower JE. Breast cancer in younger women: reproductive and late health effects of treatment. *J Clin Oncol Off J Am Soc Clin Oncol*. 2003;21(22):4184–4193. https://doi.org/10.1200/JCO.2003.04.196.
6 Sella T, Poorvu PD, Ruddy KJ, et al. Impact of fertility concerns on endocrine therapy decisions in young breast cancer survivors. *Cancer*. 2021;127(16):2888–2894. https://doi.org/10.1002/cncr.33596.
7 Quinn GP, Vadaparampil ST, Lee JH, et al. Physician referral for fertility preservation in oncology patients: a national study of practice behaviors. *J Clin Oncol Off J Am Soc Clin Oncol*. 2009;27(35):5952–5957. https://doi.org/10.1200/JCO.2009.23.0250.
8 Ben-Aharon I, Shalgi R. What lies behind chemotherapy-induced ovarian toxicity? *Reprod Camb Engl*. 2012;144(2):153–163. https://doi.org/10.1530/REP-12-0121.
9 Lambertini M, Del Mastro L, Pescio MC, et al. Cancer and fertility preservation: international recommendations from an expert meeting. *BMC Med*. 2016;14:1. https://doi.org/10.1186/s12916-015-0545-7.
10 Rodriguez-Wallberg KA, Jiang Y, Lekberg T, Nilsson HP. The late effects of cancer treatment on female fertility and the current status of fertility preservation—A narrative review. *Life*. 2023;13(5):5. https://doi.org/10.3390/life13051195.
11 Arecco L, de Moura Leite L, Gentile G, et al. Gonadotoxicity of immunotherapy and targeted agents in patients with cancer and impact on subsequent pregnancies. *Hum Reprod Oxf Engl*. 2025;40(8):1452–1466. https://doi.org/10.1093/humrep/deaf096.
12 Anderson RA, Cameron D, Clatot F, et al. Anti-Müllerian hormone as a marker of ovarian reserve and premature ovarian insufficiency in children and women with cancer: a systematic review. *Hum Reprod Update*. 2022;28(3):417–434. https://doi.org/10.1093/humupd/dmac004.
13 Chaudhri EN, Salman A, Awartani K, Khan Z, Hashmi SK. Ovarian tissue cryopreservation versus other fertility techniques for chemoradiation-induced premature ovarian insufficiency in women: a systematic review and future directions. *Life*. 2024;14(3):393. https://doi.org/10.3390/life14030393.
14 Yazdani A, Sweterlitsch KM, Kim H, Flyckt RL, Christianson MS. Surgical innovations to protect fertility from oncologic pelvic radiation therapy: ovarian transposition and uterine fixation. *J Clin Med*. 2024;13(18):5577. https://doi.org/10.3390/jcm13185577.
15 Ribeiro R, Baiocchi G, Moretti-Marques R, Linhares JC, Costa CN, Pareja R. Uterine transposition for fertility and ovarian function preservation after radiotherapy. *Int J Gynecol Cancer Off J Int Gynecol Cancer Soc*; 2023. Published online October 28: ijgc-2023-004723 https://doi.org/10.1136/ijgc-2023-004723.
16 Meistrich ML, Wilson G, Brown BW, da Cunha MF, Lipshultz LI. Impact of cyclophosphamide on long-term reduction in sperm count in men treated with combination chemotherapy for Ewing and soft tissue sarcomas. *Cancer*. 1992;70(11):2703–2712. https://doi.org/10.1002/1097-0142(19921201)70:11<2703::aid-cncr2820701123>3.0.co;2-x.
17 Meistrich ML, Chawla SP, Da Cunha MF, et al. Recovery of sperm production after chemotherapy for osteosarcoma. *Cancer*. 1989;63(11):2115–2123. https://doi.org/10.1002/1097-0142(19890601)63:11<2115::aid-cncr2820631108>3.0.co;2-a.
18 Howell SJ, Shalet SM. Spermatogenesis after cancer treatment: damage and recovery. *J Natl Cancer Inst Monogr*. 2005;(34):12–17. https://doi.org/10.1093/jncimonographs/lgi003.
19 Mitchell RT, Stukenborg JB, Jahnukainen K. Male hypogonadism due to cancer and cancer treatments. In: Winters SJ, Huhtaniemi IT, eds. *Male hypogonadism: basic, clinical and therapeutic principles*. Springer International Publishing; 2017:235–256. https://doi.org/10.1007/978-3-319-53298-1_12.
20 Duffin K, Mitchell RT, Brougham MFH, Hamer G, van Pelt AMM, Mulder CL. Impacts of cancer therapy on male fertility: past and present. *Mol Aspects Med*. 2024;100:101308. https://doi.org/10.1016/j.mam.2024.101308.
21 Su HI, Lacchetti C, Letourneau J, et al. Fertility preservation in people with cancer: ASCO guideline update. *J Clin Oncol*. 2025;JCO2402782. https://doi.org/10.1200/JCO-24-02782. Published online March 19.
22 Tuerxun H, Zhao Y, Li Y, et al. Immune checkpoint inhibitors as a threat to reproductive function: a systematic review. *Crit Rev Oncol Hematol*. 2023;188:104064. https://doi.org/10.1016/j.critrevonc.2023.104064.
23 Keller SR, Rosen A, Lewis MA, et al. Patient-reported discussions on fertility preservation before early-onset cancer treatment. *JAMA Netw Open*. 2024;7(11):e2444540. https://doi.org/10.1001/jamanetworkopen.2024.44540.
24 Lambertini M, Moore HCF, Leonard RCF, et al. Gonadotropin-releasing hormone agonists during chemotherapy for preservation of ovarian function and fertility in premenopausal patients with early breast cancer: a systematic review and meta-

analysis of individual patient-level data. *J Clin Oncol Off J Am Soc Clin Oncol*. 2018;36(19):1981–1990. https://doi.org/10.1200/JCO.2018.78.0858.
25 Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74(1):12–49. https://doi.org/10.3322/caac.21820.
26 Kehm RD, Terry MB. Early onset cancer trends and the persistently higher burden of cancer in young women. *Oncologist*. 2025;30(5):oyaf084. https://doi.org/10.1093/oncolo/oyaf084.
27 Danpanichkul P, Pang Y, Sirimangklanurak S, et al. Contemporary changes in global trends in early-onset cancer: incidence and mortality (2000–2021). *Cancers*. 2025;17(17):2766. https://doi.org/10.3390/cancers17172766.
28 Salzmann M, Tosev G, Heck M, et al. Male fertility during and after immune checkpoint inhibitor therapy: a cross-sectional pilot study. *Eur J Cancer*. 2021;152:41–48. https://doi.org/10.1016/j.ejca.2021.04.031.
29 Rabinowitz MJ, Kohn TP, Peña VN, Samarska IV, Matoso A, Herati AS. Onset of azoospermia in man treated with ipilimumab/nivolumab for BRAF negative metastatic melanoma. *Urol Case Rep*. 2021;34:101488. https://doi.org/10.1016/j.eucr.2020.101488.
30 Longo I, Sánchez-Mateos P, Lázaro P, Longo N. Azoospermia in a patient receiving interferon alpha for a stage III melanoma. *Acta Derm Venereol*. 2002;82(5):389–390. https://doi.org/10.1080/000155502320624212.
31 Karamfilov T, Wollina U, Hipler UC, Graefe T, Schreiber G. Effects of adjuvant interferon-alpha low-dose therapy in melanoma patients on serum inhibin B. *J Dermatol*. 2000;27(10):639–642. https://doi.org/10.1111/j.1346-8138.2000.tb02245.x.
32 Ghezzi M, Garolla A, Magagna S, et al. Fertility outcomes and Sperm-DNA parameters in metastatic melanoma survivors receiving vemurafenib or dabrafenib therapy: case report. *Front Oncol*. 2020;10:232. https://doi.org/10.3389/fonc.2020.00232.
33 Stensheim H, Cvancarova M, Møller B, Fosså SD. Pregnancy after adolescent and adult cancer: a population-based matched cohort study. *Int J Cancer*. 2011;129(5):1225–1236. https://doi.org/10.1002/ijc.26045.
34 Boutros A, Idan A, Sleiman S, et al. Testicular function after immune-checkpoint inhibitors treatment. *Clin Endocrinol (Oxf)*. 2025. https://doi.org/10.1111/cen.70001. Published online July 14.
35 Flatt SB, Baillargeon A, McClintock C, Pudwell J, Velez MP. Premature ovarian insufficiency in female adolescent and young adult survivors of non-gynecological cancers: a population-based cohort study. *Reprod Health*. 2023;20(1):4. https://doi.org/10.1186/s12978-022-01559-8.
36 Velez MP, Richardson H, Baxter NN, et al. Risk of infertility in female adolescents and young adults with cancer: a population-based cohort study. *Hum Reprod Oxf Engl*. 2021;36(7):1981–1988. https://doi.org/10.1093/humrep/deab036.
37 Bucheit AD, Hardy JT, Szender JB, Glitza Oliva IC. Conception and viable twin pregnancy in a patient with metastatic melanoma while treated with CTLA-4 and PD-1 checkpoint inhibition. *Melanoma Res*. 2020;30(4):423–425. https://doi.org/10.1097/CMR.0000000000000657.
38 Hartman M, Liu J, Czene K, et al. Birth rates among female cancer survivors: a population-based cohort study in Sweden. *Cancer*. 2013;119(10):1892–1899. https://doi.org/10.1002/cncr.27929.
39 Buchbinder EI, Song Z, Lee SJ, et al. Impact of immune checkpoint inhibition on ovarian reserve in patients with melanoma enrolled in the ECOG-ACRIN E1609 adjuvant trial. *J Clin Oncol*. 2023;41(16_suppl):12013. https://doi.org/10.1200/JCO.2023.41.16_suppl.12013.
40 Buchbinder EI, Song Z, Cohen JV, et al. Impact of immune checkpoint inhibition on ovarian reserve. *Oncologist*. 2026. https://doi.org/10.1093/oncolo/oyag048.
41 Weidlinger S, Graber S, Bratschi I, et al. A systematic review of the gonadotoxicity of osteosarcoma and ewing's sarcoma chemotherapies in postpubertal females and males. *J Adolesc Young Adult Oncol*. 2024;13(4):597–606. https://doi.org/10.1089/jayao.2023.0185.
42 Longhi A, Macchiagodena M, Vitali G, Bacci G. Fertility in male patients treated with neoadjuvant chemotherapy for osteosarcoma. *J Pediatr Hematol Oncol*. 2003;25(4):292–296. https://doi.org/10.1097/00043426-200304000-00005.
43 Siimes MA, Elomaa I, Koskimies A. Testicular function after chemotherapy for osteosarcoma. *Eur J Cancer*. 1990;26(9):973–975. https://doi.org/10.1016/0277-5379(90)90623-2.
44 Hibi H, Ohori T, Yamada Y, Honda N, Hashiba Y, Asada Y. Testicular sperm extraction and ICSI in patients with post-chemotherapy non-obstructive azoospermia. *Arch Androl*. 2007;53(2):63–65. https://doi.org/10.1080/01485010600915152.
45 Shamberger RC, Sherins RJ, Rosenberg SA. The effects of postoperative adjuvant chemotherapy and radiotherapy on testicular function in men undergoing treatment for soft tissue sarcoma. *Cancer*. 1981;47(10):2368–2374. https://doi.org/10.1002/1097-0142(19810515)47:10<2368::aid-cncr2820471008>3.0.co;2-d.
46 Almog B, Azem F, Gordon D, et al. Effects of cancer on ovarian response in controlled ovarian stimulation for fertility preservation. *Fertil Steril*. 2012;98(4):957–960. https://doi.org/10.1016/j.fertnstert.2012.06.007.
47 Palmert MR, Alexander SW, Goorin AM. Ovarian toxicity after chemotherapy: possible association with ifosfamide administration. *Pediatr Blood Cancer*. 2004;42(3):216–219. https://doi.org/10.1002/pbc.10320.
48 Ghazeeri G, Awwad J. Two successful pregnancies in a patient with chemotherapy-induced ovarian failure while on hormone replacement therapy. *Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol*. 2012;28(4):286–287. https://doi.org/10.3109/09513590.2011.633657.
49 Yang J, Zhen H, Hairong X, Yemei G, Xiaohui N. Chemotherapy-induced amenorrhea and its effects on fertility in long-term female survivors of classic osteosarcoma. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer*. 2021;29(10):5999–6004. https://doi.org/10.1007/s00520-021-06069-0.
50 Testolin A, Pozza F, Dal Fior S, Bolzicco GP, Panizzoni GA, Gasparini G. Surgical and adjuvant radiation therapy of resectable retroperitoneal soft tissue sarcomas in adults. *Tumori*. 1992;78(6):388–391. https://doi.org/10.1177/030089169207800609.
51 De Sanctis R, Lorenzi E, Agostinetto E, D'Amico T, Simonelli M, Santoro A. Primary ovarian insufficiency associated with pazopanib therapy in a breast angiosarcoma patient: a CARE-compliant case report. *Medicine (Baltim)*. 2019;98(50):e18089. https://doi.org/10.1097/MD.0000000000018089.
52 Gutkin PM, Chen EL, Miller CJ, et al. Successful full-term pregnancies after high-dose pelvic radiotherapy for ewing sarcoma: a case report. *J Pediatr Hematol Oncol*. 2020;42(8):e807–e809. https://doi.org/10.1097/MPH.0000000000001581.
53 Dicken CL, Lieman HJ, Dayal AK, Mutyala S, Einstein MH. A multidisciplinary approach to fertility-sparing therapy for a rare vulvar tumor. *Fertil Steril*. 2010;93(1):267.e5–267.e7. https://doi.org/10.1016/j.fertnstert.2009.07.1007.
54 Falk P, Severin M, Berglund Å, et al. Sex hormones and sperm parameters after adjuvant oxaliplatin-based treatment for colorectal cancer. *Cancer Treat Res Commun*. 2022;31:100517. https://doi.org/10.1016/j.ctarc.2022.100517.
55 Levi M, Shalgi R, Brenner B, et al. The impact of oxaliplatin on the gonads: from bedside to the bench. *Mol Hum Reprod*. 2015;21(12):885–893. https://doi.org/10.1093/molehr/gav055.
56 Hermann RM, Henkel K, Christiansen H, et al. Testicular dose and hormonal changes after radiotherapy of rectal cancer. *Radiother Oncol J Eur Soc Ther Radiol Oncol*. 2005;75(1):83–88. https://doi.org/10.1016/j.radonc.2004.12.017.
57 Buchli C, Tapper J, Bottai M, et al. Testosterone and body composition in men after treatment for rectal cancer. *J Sex Med*. 2015;12(3):774–782. https://doi.org/10.1111/jsm.12751.
58 Bruheim K, Svartberg J, Carlsen E, et al. Radiotherapy for rectal cancer is associated with reduced serum testosterone and increased FSH and LH. *Int J Radiat Oncol Biol Phys*. 2008;70(3):722–727. https://doi.org/10.1016/j.ijrobp.2007.10.043.
59 Sahin T, Dizdar O, Ozdemir N, et al. The frequency and predictors of persistent amenorrhea in premenopausal women with colorectal cancer who received adjuvant chemotherapy. *Anti Cancer Drugs*. 2019;30(3):289–294. https://doi.org/10.1097/CAD.0000000000000728.
60 Wan J, Gai Y, Li G, Tao Z, Zhang Z. Incidence of chemotherapy- and chemoradiotherapy-induced amenorrhea in premenopausal women with stage II/III colorectal cancer. *Clin Colorectal Cancer*. 2015;14(1):31–34. https://doi.org/10.1016/j.clcc.2014.09.012.
61 Cercek A, Siegel CL, Capanu M, Reidy-Lagunes D, Saltz LB. Incidence of chemotherapy-induced amenorrhea in

premenopausal women treated with adjuvant FOLFOX for colorectal cancer. *Clin Colorectal Cancer*. 2013;12(3):163–167. https://doi.org/10.1016/j.clcc.2013.04.007.
62 Holloman C, Carlan SJ, Sundharkrishnan L, Guzman A, Madruga M. Successful pregnancy after mucinous cystic neoplasm with invasive carcinoma of the pancreas in a patient with polycystic ovarian syndrome: a case report. *J Med Case Rep*. 2017;11(1):188. https://doi.org/10.1186/s13256-017-1343-y.
63 Segelman J, Buchli C, Röjvall AS, et al. Effect of radiotherapy for rectal cancer on ovarian androgen production. *Br J Surg*. 2019;106(3):267–275. https://doi.org/10.1002/bjs.10980.
64 Aasebø U, Bremnes RM, Aakvaag A, Slørdal L. Gonadal endocrine dysfunction in patients with lung cancer: relation to responsiveness to chemotherapy, respiratory function and performance status. *J Steroid Biochem Mol Biol*. 1991;39(3):375–380. https://doi.org/10.1016/0960-0760(91)90049-b.
65 Aasebø U, Slørdal L, Aanderud S, Aakvaag A. Chemotherapy and endocrine function in lung cancer. *Acta Oncol Stockh Swed*. 1989;28(5):667–669. https://doi.org/10.3109/02841868909092291.
66 Laguna JC, Tagliamento M, Lambertini M, Hiznay J, Mezquita L. Tackling non-small cell lung cancer in young adults: from risk factors and genetic susceptibility to lung cancer profile and outcomes. *Am Soc Clin Oncol Educ Book*. 2024;44(3):e432488. https://doi.org/10.1200/EDBK_432488.
67 Mawet M, Basse C, Barrois M, et al. Second-trimester medical abortion after exposure to lorlatinib during early pregnancy, a case report. *J Gynecol Obstet Hum Reprod*. 2023;52(10):102673. https://doi.org/10.1016/j.jogoh.2023.102673.
68 Shen L, Xu W, Gao J, et al. Pregnancy after the diagnosis of lymphangioleiomyomatosis (LAM). *Orphanet J Rare Dis*. 2021;16(1):133. https://doi.org/10.1186/s13023-021-01776-7.
69 Merideth MA, Harney LA, Vyas N, et al. Gynecologic and reproductive health in patients with pathogenic germline variants in DICER1. *Gynecol Oncol*. 2020;156(3):647–653. https://doi.org/10.1016/j.ygyno.2019.12.037.
70 Cathcart-Rake EJ, Ruddy KJ, Gupta R, et al. Amenorrhea after lung cancer treatment. *Menopause*. 2019;26(3):306–310. https://doi.org/10.1097/GME.0000000000001199.
71 Cohen MM, Freyer AM, Johnson SR. Pregnancy experiences among women with lymphangioleiomyomatosis. *Respir Med*. 2009;103(5):766–772. https://doi.org/10.1016/j.rmed.2008.11.007.
72 Luke B, Brown MB, Missmer SA, et al. Assisted reproductive technology use and outcomes among women with a history of cancer. *Hum Reprod Oxf Engl*. 2016;31(1):183–189. https://doi.org/10.1093/humrep/dev288.
73 Hallak J, Mahran A, Chae J, Agarwal A. The effects of cryopreservation on semen from men with sarcoma or carcinoma. *J Assist Reprod Genet*. 2000;17(4):218–221. https://doi.org/10.1023/a:1009443901307.
74 Hovav Y, Dan-Goor M, Yaffe H, Almagor M. Electroejaculation before chemotherapy in adolescents and young men with cancer. *Fertil Steril*. 2001;75(4):811–813. https://doi.org/10.1016/s0015-0282(01)01680-6.
75 Rothmann SA, Schroeder-Jenkins M, Henrich L, Thomas AJ. Twin pregnancy using cryopreserved sperm from a man with chondrosarcoma. *Cleve Clin Q*. 1986;53(1):95–97. https://doi.org/10.3949/ccjm.53.1.95.
76 Shin T, Kobayashi T, Shimomura Y, et al. Microdissection testicular sperm extraction in Japanese patients with persistent azoospermia after chemotherapy. *Int J Clin Oncol*. 2016;21(6):1167–1171. https://doi.org/10.1007/s10147-016-0998-5.
77 Courbiere B, Decanter C, Bringer-Deutsch S, et al. Emergency IVF for embryo freezing to preserve female fertility: a French multicentre cohort study. *Hum Reprod Oxf Engl*. 2013;28(9):2381–2388. https://doi.org/10.1093/humrep/det268.
78 Cioffi R, Pagliardini L, Quartucci A, et al. Response to controlled ovarian stimulation is not impaired in young patients with a sarcoma: results from a monocentric case-control study. *Cancers*. 2023;15(12):3141. https://doi.org/10.3390/cancers15123141.
79 Ernst E, Bergholdt S, Jørgensen JS, Andersen CY. The first woman to give birth to two children following transplantation of frozen/thawed ovarian tissue. *Hum Reprod Oxf Engl*. 2010;25(5):1280–1281. https://doi.org/10.1093/humrep/deq033.
80 Mohsenzadeh M, Khalili MA, Tabibnejad N, Yari N, Agha-Rahimi A, Karimi-Zarchi M. Embryo cryopreservation following In-Vitro maturation for fertility preservation in a woman with Mullerian adenosarcoma: a case report. *J Hum Reprod Sci*. 2017;10(2):138–141. https://doi.org/10.4103/jhrs.JHRS_93_16.
81 Kayiira A, Neda John J, Zaake D, et al. Understanding fertility attitudes and outcomes among survivors of adolescent and young adult cancers in a low-resource setting: a registry-based computer-assisted telephone interview survey. *J Adolesc Young Adult Oncol*. 2023;12(4):520–528. https://doi.org/10.1089/jayao.2022.0114.
82 von Wolff M, Bruckner T, Strowitzki T, Germeyer A. Fertility preservation: ovarian response to freeze oocytes is not affected by different malignant diseases-an analysis of 992 stimulations. *J Assist Reprod Genet*. 2018;35(9):1713–1719. https://doi.org/10.1007/s10815-018-1227-0.
83 Pening D, Constant M, Bruynbroeck M, Delbaere A, Demeestere I. Impact of cancer on cryopreserved sperm quality and fertility: a cohort study. *Health Sci Rep*. 2022;5(4):e726. https://doi.org/10.1002/hsr2.726.
84 Alvarez RM, Ramanathan P. Fertility preservation in female oncology patients: the influence of the type of cancer on ovarian stimulation response. *Hum Reprod Oxf Engl*. 2018;33(11):2051–2059. https://doi.org/10.1093/humrep/dew158.
85 Stupart D, Win AK, Winship IM, Jenkins M. Fertility after young-onset colorectal cancer: a study of subjects with Lynch syndrome. *Colorectal Dis*. 2015;17(9):787–793. https://doi.org/10.1111/codi.12940.
86 Selter J, Huang Y, Williams SZ, et al. Use of fertility preservation services in male reproductive-aged cancer patients. *Gynecol Oncol Rep*. 2021;36:100716. https://doi.org/10.1016/j.gore.2021.100716.
87 Barahmeh S, Al Masri M, Badran O, et al. Ovarian transposition before pelvic irradiation: indications and functional outcome. *J Obstet Gynaecol Res*. 2013;39(11):1533–1537. https://doi.org/10.1111/jog.12096.
88 Sioulas VD, Jorge S, Chern JY, et al. Robotically assisted laparoscopic ovarian transposition in women with lower gastrointestinal cancer undergoing pelvic radiotherapy. *Ann Surg Oncol*. 2017;24(1):251–256. https://doi.org/10.1245/s10434-016-5650-0.
89 Turkgeldi L, Cutner A, Turkgeldi E, et al. Laparoscopic ovarian transposition and ovariopexy for fertility preservation in patients treated with pelvic radiotherapy with or without chemotherapy. *Facts Views Vis ObGyn*. 2019;11(3):235–242.
90 Farber LA, Ames JW, Rush S, Gal D. Laparoscopic ovarian transposition to preserve ovarian function before pelvic radiation and chemotherapy in a young patient with rectal cancer. *MedGenMed*. 2005;7(1):66.
91 Gavrilova-Jordan L, Rowe MS, Ballenger CA, Mersereau JE, Hayslip CC. Emergent oocyte cryopreservation with a novel ovarian transposition technique in a colorectal cancer patient: a combined approach for fertility preservation. A case report. *J Reprod Med*. 2015;60(7–8):354–358.
92 Lohynska R, Jirkovska M, Novakova-Jiresova A, et al. Radiotherapy dose limit for uterus fertility sparing in curative chemoradiotherapy for rectal cancer. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2021;165(1):99–101. https://doi.org/10.5507/bp.2020.039.
93 Hilal L, Cercek A, Navilio J, et al. Factors associated with premature ovarian insufficiency in young women with locally advanced rectal cancer treated with pelvic radiation therapy. *Adv Radiat Oncol*. 2022;7(1):100801. https://doi.org/10.1016/j.adro.2021.100801.
94 Lopez A, Perez Villena JF, Guevara Jabiles A, Davila K, Sernaque Quintana R, Ribeiro R. Uterine transposition and successful pregnancy in a patient with rectal cancer. *Int J Gynecol Cancer*. 2023;33(8):1310–1315. https://doi.org/10.1136/ijgc-2023-004661.
95 Di Tucci C, Galati G, Mattei G, Chinè A, Fracassi A, Muzii L. Fertility after cancer: risks and successes. *Cancers*. 2022;14(10):2500. https://doi.org/10.3390/cancers14102500.
96 Gentile G, Scagnoli S, Arecco L, Santini D, Botticelli A, Lambertini M. Assessing risks and knowledge gaps on the impact of systemic therapies in early breast cancer on female fertility: a systematic review of the literature. *Cancer Treat Rev*. 2024;128:102769. https://doi.org/10.1016/j.ctrv.2024.102769.
97 Hazzard TM, Stouffer RL. Angiogenesis in ovarian follicular and luteal development. *Baillieres Best Pract Res Clin Obstet Gynaecol*. 2000;14(6):883–900. https://doi.org/10.1053/beog.2000.0133.
98 Letourneau JM, Ebbel EE, Katz PP, et al. Acute ovarian failure underestimates age-specific reproductive impairment for young women undergoing chemotherapy for cancer. *Cancer*. 2012;118(7):1933–1939. https://doi.org/10.1002/cncr.26403.

99 Köylü B, Esen BH, Bektaş ŞN, et al. Pharmacovigilance analysis of immune checkpoint inhibitor-related reproductive adverse effects based on the FDA adverse event reporting system. *Sci Rep*. 2025;15(1):7770. https://doi.org/10.1038/s41598-025-91476-0.

100 Shiraishi K, Matsuyama H. Microdissection testicular sperm extraction and salvage hormonal treatment in patients with postchemotherapy azoospermia. *Urology*. 2014;83(1):100–106. https://doi.org/10.1016/j.urology.2013.08.043.

101 Azem F, Amit A, Merimsky O, Lessing JB. Successful transfer of frozen-thawed embryos obtained after subtotal colectomy for colorectal cancer and before fluorouracil-based chemotherapy. *Gynecol Oncol*. 2004;93(1):263–265. https://doi.org/10.1016/j.ygyno.2003.12.030.

102 Cui W, Rocconi RP, Thota R, et al. Measuring ovarian toxicity in clinical trials: an American Society of Clinical Oncology research statement. *Lancet Oncol*. 2023;24(10):e415–e423. https://doi.org/10.1016/S1470-2045(23)00390-X.

103 Khalifa E, Oehninger S, Acosta AA, et al. Successful fertilization and pregnancy outcome in in-vitro fertilization using cryopreserved/thawed spermatozoa from patients with malignant diseases. *Hum Reprod Oxf Engl*. 1992;7(1):105–108. https://doi.org/10.1093/oxfordjournals.humrep.a137539.

104 Fu L, Zhou F, An Q, et al. Sperm cryopreservation for Male cancer patients: more than 10 years of experience, in Beijing China. *Med Sci Monit Int Med J Exp Clin Res*. 2019;25:3256–3261. https://doi.org/10.12659/MSM.913513.

105 Hoshi M, Takami M, Ieguchi M, et al. Fertility following treatment of high-grade malignant bone and soft tissue tumors in young adults. *Mol Clin Oncol*. 2015;3(2):367–374. https://doi.org/10.3892/mco.2014.474.

106 Ribeiro R, Anselmi MC, Schneider GA, Rodrigues Furtado JP, Mohamed Abau Shwareb MG, Linhares JC. First live birth after uterine transposition. *Fertil Steril*. 2023;120(1):188–193. https://doi.org/10.1016/j.fertnstert.2023.02.033.

107 Sako Y, Akitani F, Shiota K, Momoeda M. A case of two ovarian tissue transplantations that led to a biochemical pregnancy in Japan. *J Obstet Gynaecol Res*. 2022;48(5):1279–1284. https://doi.org/10.1111/jog.15192.

108 Rodriguez-Wallberg KA, Karlström PO, Rezapour M, et al. Full-term newborn after repeated ovarian tissue transplants in a patient treated for ewing sarcoma by sterilizing pelvic irradiation and chemotherapy. *Acta Obstet Gynecol Scand*. 2015;94(3):324–328. https://doi.org/10.1111/aogs.12568.

109 Dong R, Pang Y, Mao H, Yang N, Liu P. Successful pregnancy following conservative management of low-grade endometrial stromal sarcoma: a case report. *Oncol Lett*. 2014;7(4):1039–1042. https://doi.org/10.3892/ol.2014.1858.

110 Morice P, Castaigne D, Haie-Meder C, et al. Laparoscopic ovarian transposition for pelvic malignancies: indications and functional outcomes. *Fertil Steril*. 1998;70(5):956–960. https://doi.org/10.1016/s0015-0282(98)00284-2.

111 Buchli C, Al Abani M, Ahlberg M, et al. Assessment of testicular dose during preoperative radiotherapy for rectal cancer. *Acta Oncol Stockh Swed*. 2016;55(4):496–501. https://doi.org/10.3109/0284186X.2015.1073349.

112 Rozen G, Chander S, Polyakov A, Thevathasan I, Stern CJ. Live birth from ovarian grafted tissue after pelvic radiation for rectal cancer. *FS Rep*. 2024;5(2):214–218. https://doi.org/10.1016/j.xfre.2024.04.004.

113 Michaan N, Ben-David G, Ben-Yosef D, et al. Ovarian stimulation and emergency in vitro fertilization for fertility preservation in cancer patients. *Eur J Obstet Gynecol Reprod Biol*. 2010;149(2):175–177. https://doi.org/10.1016/j.ejogrb.2009.12.023.

114 Post-operative functional outcomes in early age onset rectal cancer. *Front Oncol*. 2022;12:868359. https://doi.org/10.3389/fonc.2022.868359.

115 Zhou B, Kwan B, Desai MJ, et al. Association of platinum-based chemotherapy with live birth and infertility in female survivors of adolescent and young adult cancer. *Fertil Steril*. 2024;121(6):1020–1030. https://doi.org/10.1016/j.fertnstert.2024.01.039.

116 Gareer W, Gad Z, Gareer H. Needle oophoropexy: a new simple technique for ovarian transposition prior to pelvic irradiation. *Surg Endosc*. 2011;25(7):2241–2246. https://doi.org/10.1007/s00464-010-1541-9.

117 Al-Badawi IA, Al-Aker M, AlSubhi J, et al. Laparoscopic ovarian transposition before pelvic irradiation: a Saudi tertiary center experience. *Int J Gynecol Cancer*. 2010;20(6):1082–1086. https://doi.org/10.1111/IGC.0b013e3181e2ace5.

118 Treissman MJ, Miller D, McComb PF. Laparoscopic lateral ovarian transposition. *Fertil Steril*. 1996;65(6):1229–1231. https://doi.org/10.1016/s0015-0282(16)58344-7.

119 Köhler C, Marnitz S, Biel P, Cordes T. Successful delivery in a 39-Year-Old patient with anal cancer after fertility-preserving surgery followed by primary chemoradiation and low anti-Mullerian hormone level. *Oncology*. 2016;91(5):295–298. https://doi.org/10.1159/000449416.

120 Chae-Kim J, Hayslip CCJ. Fertility and endocrine preservation in the management of colorectal cancer in women. *Dis Colon Rectum*. 2020;63(6):723–726. https://doi.org/10.1097/DCR.0000000000001687.

121 Lee JR, Lee D, Park S, et al. Successful in vitro fertilization and embryo transfer after transplantation of cryopreserved ovarian tissue: report of the first Korean case. *J Korean Med Sci*. 2018;33(21):e156. https://doi.org/10.3346/jkms.2018.33.e156.

122 Milgrom SA, Vargas HA, Sala E, Kelvin JF, Hricak H, Goodman KA. Acute effects of pelvic irradiation on the adult uterus revealed by dynamic contrast-enhanced MRI. *Br J Radiol*. 2013;86(1031):20130334. https://doi.org/10.1259/bjr.20130334.

123 Mariani S, Chiloiro G, Villa P, et al. Fertility preservation in chemo-radiotherapy for rectal cancer: a combined approach. *Clin Transl Radiat Oncol*. 2019;19:77–79. https://doi.org/10.1016/j.ctro.2019.09.002.

124 Ribeiro R, Rebolho JC, Tsumanuma FK, Brandalize GG, Trippia CH, Saab KA. Uterine transposition: technique and a case report. *Fertil Steril*. 2017;108(2):320–324.e1. https://doi.org/10.1016/j.fertnstert.2017.06.016.

125 Kurt M, Uncu G, Cetintas SK, Kucuk N, Guler S, Ozkan L. Successful spontaneous pregnancy in a patient with rectal carcinoma treated with pelvic radiotherapy and concurrent chemotherapy: the unique role of laparoscopic lateral ovary transposition. *Eur J Gynaecol Oncol*. 2007;28(5):408–410.

126 Al-Asari S, Abduljabbar A. Laparoscopic ovarian transposition before pelvic radiation in rectal cancer patient: safety and feasibility. *Ann Surg Innov Res*. 2012;6(1):9. https://doi.org/10.1186/1750-1164-6-9.

127 Su HI, Connell MW, Bazhenova LA. Ovarian stimulation in young adult cancer survivors on targeted cancer therapies. *Fertil Steril*. 2016;106(6):1475–1478. https://doi.org/10.1016/j.fertnstert.2016.08.011.