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Systematic Review of the Gonadotoxicity and Risk of Infertility of Soft Tissue Sarcoma Chemotherapies in Pre- and Postpubertal Females and Males

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Increasing awareness of gonadotoxicity in cancer treatments and infertility risk is essential for counseling young cancer patients. While fertility preservation options are available in many countries, limited data on gonadotoxicity hinder recommendations, especially for soft tissue cancers. This review, part of the FertiTOX project (www.fertitox.com), organized by FertiPROTEKT (www.fertiprotekt.com), aims to address this knowledge gap to improve fertility preservation guidance.

We performed a systematic literature search on gonadotoxicity in soft tissue sarcoma (STS) cancer treatments. Only patients without metastases or recurrent disease were considered. "Suspected infertility" was defined based on low ovarian reserve parameters, low inhibin B levels, high gonadotropin concentration, gonadal dysfunction, amenorrhea, oligomenorrhea, azoospermia, or oligozoospermia due to limited infertility data. The study quality was assessed using the Newcastle–Ottawa Scale.

The search yielded 3309 abstracts, with 138 undergoing full-text analysis. Eight studies on STS were included. Suspected infertility was observed in 20 of 28 females (71.4%, range 0–100%) and 38 of 63 males (60.3%, range 34.8–100%) with STS. Six of the eight studies received high-quality scores on the NOS, while two received a fair score.

Our data suggest a high risk of infertility from chemotherapy in pre- and postpubertal STS survivors. This underscores the importance of considering fertility preservation measures when counseling these patients.

Keywords: fertitox, fertiprotekt, soft tissue sarcoma (STS), chemotherapy, gonadotoxicity, suspected infertility

Introduction

Soft tissue sarcoma (STS) encompasses a heterogenous group of solid tumors of mesenchymal origin.[1] STS accounts for approximately 1% of all malignant tumors in adults and about 8% of malignant tumors in children.[2] The most prevalent histological subtype is rhabdomyosarcoma in children[3] and liposarcomas, leiomyosarcomas, or undifferentiated pleomorphic sarcoma in adults.[4] They are often characterized by an aggressive tumor biology. However, there has been a marked improvement in prognosis in recent years, driven by advances in cancer treatment.[4] Advances in medical science have led to improved 5-year survival rates for STS, approximately 73%.[5]

Therefore, fertility preservation has become an increasing concern[6] and medical guidelines and clinical practice take fertility preservation more and more into account. However, most

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current clinical practice guidelines for STS, such as those from ESMO,[7] ASCO,[8] or NCCN,[1] do not address fertility preservation. The ESMO[9] and ESHRE[10] fertility preservation guidelines do not provide specific information on fertility preservation assessment or recommendations for STS, unlike the entity of osteosarcoma and Ewing sarcoma. The handbook of the network FertiPROTEKT is one of the few sources that contain specific recommendations for fertility preservation in soft tissue tumors.[11]

Data on the gonadotoxicity of chemotherapies for STS are very limited. This limitation is of clinical significance as oncologists as well as reproductive physicians need to estimate the risk of infertility when they counsel patients about fertility preservation measures. Although the gonadotoxicity of specific chemotherapies can be estimated using risk calculators, which are even available online (www.oncofertilityrisk.com), the risk of infertility also needs to be provided on a disease-specific basis. The specific chemotherapy and its total dosage may not be defined at the time of fertility preservation counseling, the chemotherapy may even be adjusted during the course of therapy, and the accuracy of the prediction still needs to be validated. It is therefore of great clinical importance for reproductive physicians to be able to provide estimates of gonadotoxicity and the expected risk of infertility to be able to advise patients on fertility preservation measures.

We therefore aimed to analyze the current state of evidence regarding gonadotoxicity associated with chemotherapy treatment of STS. The review is part of the FertiTOX project[12] (www.fertitox.com), organized by FertiPROTEKT (www.fertiprotekt.com), which aims to fill the data gap on gonadotoxicity of cancer therapies to enable more accurate counseling regarding fertility preservation.[13,14] Only females and males without metastases or recurrent disease were considered. Due to the frequent prevalence of STS in children and adolescents, studies with prepubertal cancer patients were also included.

Materials and Methods

Protocol registration

Our study protocol was registered at the international Prospective Register of Systematic Reviews, PROSPERO (Registry number CRD42023385402). The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA)[15] were used. The FertiTOX project[12] and the associated retrospective and prospective data analyses have been approved by all Swiss ethics committees.

Sources and search strategy

A complex literature search was designed and conducted in the medical bibliographic databases MEDLINE via Embase and Cochrane Library to identify relevant documents on the topic. For the update search, the 50 most relevant references were downloaded from Google Scholar and manually compared with the previous references. In addition, forward and backward citation tracking was performed for individual studies. The original search was performed in December 2022 and the last updated on February 8, 2024.

A primary literature search strategy was developed in Embase by a medical information specialist and tested against a list of key references. Following refinement and consultation, complex search strategies were created for each information source based on database-specific controlled vocabulary (thesaurus terms/subject headings) and text words. Synonyms, acronyms, and similar terms were included in the textword search. The search was restricted to publications since 2000.

The search terms used were as follows: (1). soft tissue neoplasm (myosarcoma, leiomyosarcoma, liposarcoma, nerve sheet neoplasm, angiosarcoma); (2) cancer treatment (chemotherapy, radiotherapy); and (3) gonadotoxic effects or impact on fertility parameters. Studies involving only animals, plants, or fungi were excluded from the MEDLINE and Embase searches using a double-negative search strategy based on Ovid's "humans-only" filters. The detailed final search strategies are presented in Supplementary Data S1. In addition to the electronic database searches, reference lists and bibliographies of relevant publications were reviewed for relevant studies.

Study selection process

The identified citations were imported into Deduklick[16] and duplicates were removed. Three investigators (MS, AR, and FP) performed the screening of titles and abstracts and tested against the inclusion and exclusion criteria (Table 1) using the Covidence software (www.covidence.org).[17] Cancer treatments were assessed on their gonadotoxicity. Gonadotoxicity with clinical relevance was defined as suspected infertility, subdefined by the criteria in Table 2.

Data extraction

Three investigators (MS, AR, and FP) independently abstracted and reviewed the extracted data in detail. Key variables of interest were as follows: characteristics of the study populations (study design, age and number of patients at diagnosis and outcome, length of follow-up), tumor (type, localization), oncological treatment (applied regimen and dose of chemotherapy), and fertility parameters (Table 4). Discrepancies were discussed and resolved by consensus.

Quality assessment

We assessed the quality of each study using the Newcastle–Ottawa Scale.[18] The following three parameters were considered for the scoring of the individual study: subject selection (0–4 stars), comparability (0–2 stars), and study outcome (0–3 stars). The rating consisted of the following: good quality (= 3 or 4 stars

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria
• Any original articles with information on cancer type, oncological therapy, and fertility outcomes (as shown in Table 2).
• Articles in which fertility data were analyzed and described separately for the different cancer types and for females and males
Exclusion criteria
• Patients >40 years of age at the time of potential gonadotoxic therapy
• Patients with cancer relapse and palliative treatment
• Patients with stem cell transplantation
• Females with radiotherapy of the pelvis
• Males with radiotherapy on the testicles

Table 2. Definition of Suspected Infertility

Females:
- Menstrual cycle disorders (amenorrhea, oligomenorrhea)
- Gonadotropins (follicle stimulating hormone, FSH; luteinizing hormone, LH) above the normal range
- Low anti-Müllerian hormone (AMH)
- Premature ovarian insufficiency (POI)
- Low ovarian reserve parameters (antral follicle count, follicle density, ovarian surface)
- Gonadal dysfunction

Males:
- Significant reduction in sperm quality (azoospermia, oligozoospermia)
- Gonadotropins (follicle stimulating hormone, FSH; luteinizing hormone, LH) above the normal range
- Inhibin B, below normal range
- Gonadal dysfunction

in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain), fair quality (= 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain), and poor quality (= 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 star in outcome/exposure domain).

To independently assess the risk of bias, all included studies were reviewed by MS, AR, and FP. Disagreements were resolved by consensus. Six[19–24] of the eight studies were rated good, corresponding to a low risk of bias. The study of Rendtorff et al. (2012)[25] and Kenney et al. (2001)[26] got a lower rating in terms of a fair-quality score due to lacking a comparison group, no evidence about the outcome not being present at study start and limited follow-up (Table 3).

Results

Study characteristics

The database search yielded a total of 3309 abstracts, 138 of which were included in the full-text analysis (Fig. 1). Of these, 8 studies, each on STS, could be included in the review (Table 4, Fig. 1). The Embase database yielded the most abstracts, followed by Medline and Cochrane. The main reasons for excluding the 3164 abstracts were lack of clear reference to fertility, lack of subdivision by tumor entity, and lack of an original work. The 8 reviewed studies reported anti-Müllerian hormone (AMH), ovarian reserve parameters, gonadotropin values, and gonadal dysfunction as female fertility outcomes. Male fertility parameters included sperm quality, inhibin B levels, gonadotropins, testicular volume, and gonadal dysfunction. Four studies were conducted with males, 3 with females, and 1 with both genders. The study size in studies with females varied from 22 to 561 cancer survivors, of which 1 to 16 were STS patients. In studies with males, the number of participants ranged from 17 to 561, of which 2 to 23 were STS patients. The studies examined included a total of 28 females and 63 males with STS.

The age structure at diagnosis or start of treatment varied from <1 to 14 years for females and from <1 to 21 years for males. As a result, most of the participants were prepubertal, although the puberty status was not stated for each participant. Certain information, such as follow-up duration, age at

Table 3. Newcastle–Ottawa Quality Assessment Form for Cohort Studies

	Selection				*Comparability*	*Outcome*				
Study	*Representativeness of exposed cohort*	*Selection of nonexposed cohort*	*Ascertainment of exposure*	*Outcome of interest not present at study start*	*Comparability of cohorts on the basis of the design or analysis controlled for confounders*	*Assessment of outcome*	*Sufficient length of follow-up for outcomes to occur*	*Adequacy of follow-up of cohorts*	*Total*	*Quality assessment*	*Comments*
Abaza, 2015	★	★	★★	—	★★	★★	★★	—	6/8	Good	
Brougham, 2012	★★	—	★★	★	★★	★★	★★	★	7/8	Good	
Kenney, 2001	★★	—	★★	—	★★	★★	★★	—	5/8	Fair	No comparison group, no demonstration that outcome was present at diagnosis/start, follow-up less than 80%
Latoch, 2022	★★	—	★★	★★	★★	★★	★★	★	7/8	Good	
Oktem, 2007	★★	★	★★	—	★★	★★	★★	—	7/8	Good	
Rendtorff, 2012	★★	—	★★	—	★★	★★	★★	—	5/8	Fair	No comparison group, no demonstration that outcome was present at start/diagnosis, no statement on follow-up
Thomas-Teinturier, 2015	★	★	★	★	★	★	★	—	7/8	Good	
Van Dorp, 2013	★	★	★	★	★	★	★	—	7/8	Good	

Table 4. Characteristics of the Included Studies

First author, year of publication	*Identification of participants of interest (cases, females/males, pubertal status at time of diagnosis/therapy)*	*Number of participants of interest*	*Age of participants of interest at time of diagnosis/therapy*	*Diagnosis/treatment period*	*Follow-up after diagnosis/ treatment, in years (range)*	*Treatment protocols*	*Reported outcome parameter and outcome*	*% suspected infertility*	*Comments*
Females									
Oktem et al., 2007	26 females with fertility preservation Inclusion: 1 synovial tissue sarcoma, pubertal status unclear	1 female	14y	Not known	10y	1st CT contained VACA: Vincristine, actinomycin D, cyclophosphamide, doxorubicin. 2nd CT contained ifosfamide and etoposide	Follicle density: follicle density was determined per mm2 of tissue surface and a mean value was obtained from all sections. No reference/range, FSH	1/1 (100%)	No healthy controls, most had cancer, possibly underestimation of the effect of cancer disease on ovarian reserve
Brougham et al., 2012	22 females with cancer, 6 RMS, inclusion of patient number 9, prepubertal, exclusion other 5 patients (metastatic situation, radiotherapy of ovaries or missing AMH-value)	1 female	2.4y	2003–2007	2 and 12 months after completing treatment and beyond 12 months Patient 9: 31 months	CT contained ifosfamide	AMH	0/1 (0%)	Single case, prepubertal, exact time line (AMH measure) and value missing
Thomas-Teinturier et al., 2015	105 female survivors of childhood cancer, sixteen with STS. Pubertal Status: 62% prepubertal, 13% during puberty, 25% postpubertal	16 females	Cancer group: Median age 9.3 y, Range 0.04–17.7y Sarcoma group: Median age 6.3 y, Range 0.1.–16.9y	Not known	Not known	CT contained ifosfamide, cyclophosphamide, procarbazine	AMH, FSH, AFC/total number of follicles (2-10mm), ovarian surface (OS) per ovary (cm2)	16/16 (100%)	*P* values, no numeric values. Lower levels (AMH, OS, etc.) confirmed by comparative analysis with published normal values.
Latoch et al., 2022	561 long-term childhood cancer survivors, 35 with STS and 2 cases with missing data = 33 in total: 23 males, 10 females, all prepubertal (<3 y)	10 females	All <3 y: Median age at diagnosis/start of treatment: 1.8 y Range 0.03-3.0y. Sarcoma Group: - <1 y: 4 - >1 < 2 y: 12 - >2 < 3 y: 19	1991–2016	Minimum latency between therapy/diagnosis and testing/study inclusion: 5 y. Median follow-up from cessation of therapy: 9.85 y Range 5.0–23.6y	All had CT according to international protocols approved by Polish Solid Tumor Group, not specified	Gonadal dysfunction: Baseline blood analysis included assessment of gonads	3/10 (30.3%)	Outcome "gonadal dysfunction", not further specified. Study with females and males, see also male table
Males									
Kenney et al., 2001	17 adult male survivors of childhood sarcomas, Thirteen cases with STS: -7 prepubertal - 6 pubertal/ postpubertal	13 males	Median age 12 y, range 4–19 y	1960–1992	Range 5–22 y, median 12 y	8 patients: VAC (Vincristine, actinomycin, cyclophosphamide) 5 patients: Adria-VAC (doxorubicin, vincristine, actinomycin, cyclophosphamide)	Testicular Volume, semen analysis, sperm fructose, FSH, LH, FSH and LH after GnRH stimulation, testosterone	11/13 (84.6%)	2 of the 11 patients possibly received some radiation of testis (lumbar and femur RT)

(*continued*)

TABLE 4. (CONTINUED)

First author, year of publication	*Identification of participants of interest (cases, females/males, pubertal status at time of diagnosis/therapy)*	*Number of participants of interest*	*Age of participants of interest at time of diagnosis/therapy*	*Diagnosis/treatment period*	*Follow-up after diagnosis/ treatment, in years (range)*	*Treatment protocols*	*Reported outcome parameter and outcome*	*% suspected infertility*	*Comments*
Rendtorff et al., 2012	77 males with cancer in childhood, 5 cases with STS: 2 of 3 had semen and hormonal analysis. Pubertal status: postpubertal, all >18 y	2 males	Average age 10 y, range 1–18 y	The participants had been treated for an oncological disease in childhood or adolescence in since 1980	Age at diagnosis sarcoma group: -Pat. 1: 12 y (tested 7 y after cancer diagnosis)- Pat. 2: 12 y (tested 24 y after cancer diagnosis)	Oncological treatment in childhood, no specification	Semen analysis, FSH, LH, inhibin B	2/2 (100%)	Both patients had hormonal analysis and semen analysis, bias should be low. The only study who used the outcome "suspected infertility"
Van Dorp et al., 2013	201 male survivors of childhood cancer: 10 cases with RMS, pubertal status not known	10 males	Median age 6 y, range 0.0–17.5y	1964–2005	Median follow-up 15.7 y, range 3.0–37.0y. Median interval between 1st (T1) and 2nd measurement (T2) 3.3 y, range 0.7–11.3y	Whole study group had CT, not specified. Seventy-eight of 201 (38.8%) patients didn't get alkylating agents (but other CT)	Inhibin B (reference level: 150–400 ng/L)	10/10 (100%)	
Abaza et al., 2014	106 STS cases:-70 males, semen analysis in 15 patients - 36 females (no outcome). Pubertal status not known (most patients <10 y, max. 21 y)	15 males	All <40 y. Most patients < 10 y, max. 21 y old: - <10 y: $n = 64$ - >10 y $n = 42$	2004–2014	Follow-up: 1 month after treatment, then every 3 months for 1st 2 y, every 6 months for 3 y, then annually. Follow-up time ranged from 5 to 80 months, median 38 months	Patients received VAC regimen: Vincristine, actinomycin D, cyclophosphamide	Semen analysis	7/15 (46.7%)	
Latoch et al., 2022	561 long-term childhood cancer survivors, 35 cases with STS, 2 with missing data, in total 33 cases: 23 males, 10 females, all prepubertal (<3 y)	23 males	All <3 y: Median age at diagnosis/start of treatment: 1.8 y Range 0.03-3.0y Sarcoma Group: - <1 y: $n = 4$ - >1 < 2 y: $n = 12$ - >2 < 3 y: $n = 19$	1991–2016	Minimum latency between therapy/diagnosis and testing/study inclusion: 5 y Median follow-up time from cessation of therapy (whole group): 9.8 y, range 5.0–23.6y	All received CT according to international protocols approved by Polish Solid Tumor Group, not specified	Gonadal dysfunction: Baseline blood analyses included assessment of gonads	8/23 (34.8%)	Outcome "gonadal dysfunction," not further specified. Study with females and males, see also female table

AMH, anti-Müllerian hormone; LH, luteinizing hormone; AFC, antral follicle count; RMS, rhabdomyosarcoma; CT, chemotherapy; RT, radiotherapy; FSH, follicle-stimulating hormone; STS, soft tissue sarcoma; GnRH, gonadotropin-releasing hormone; Y, year/s.

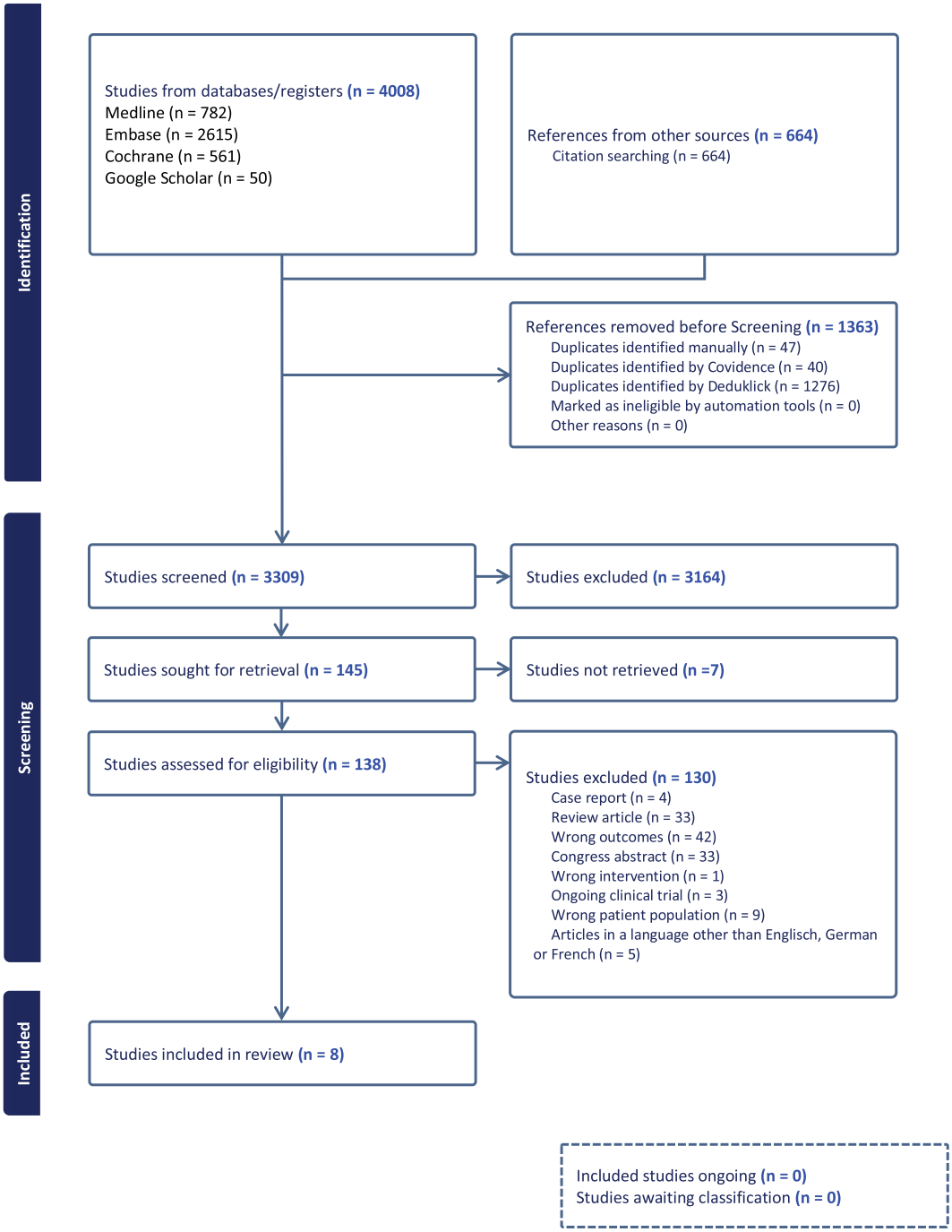

FIG. 1. Identification of studies via databases and registers.

diagnosis, or the treatment regimen used, applied to the entire study population in certain studies, which in some cases included heterogeneous tumor entities. Specific information on the STS patients was sometimes missing. As a result, this information may be slightly different for the subset of patients included in the analysis.

Data analysis

Suspected infertility was seen in 20 of 28 (71.4%, range 0–100%) of female (4 studies)[20–23] and in 38 of 63 (60.3%, range 34.8–100%) of male (5 studies)[19,21,24–26] STS patients (Table 4). Of the 8 studies, 5 studies[19,20,22,23,26] contained information on the chemotherapeutic agent used, always alkylants such as cyclophosphamide or ifosfamide. One study,[24] used the alkylating agent dose score ADD, with 61.2% of cancer survivors receiving an alkylating agent and 38.8% receiving chemotherapy without alkylating agents. The remaining 2 studies[21,25] did not contain specific information on the chemotherapeutic agent used and referred, in part, to common protocols, for example, to internationally recognized chemotherapy protocols.[21] The study of Rendtorff et al.[25] is the only one of the studies to use the term "suspected infertility;" however, the study

was small and included only one female cancer survivor after STS. The extent of suspected infertility varied between the studies, although most of them showed that it was present. Only 1 study[20] showed no fertility impairment after chemotherapeutic treatment of soft tissue cancer. The data analysis shows a higher level of suspected infertility in the studies with females (71.4%) compared with those with males (60.3%).

Discussion

The aim of this review was to analyze the data on gonadotoxicity of chemotherapy for STS and to contribute to the improvement of fertility counseling in this context. Our data suggest that chemotherapeutic treatment of STS carries a high risk for fertility in both pre- and postpubertal females and males.

Our review has some strengths that should be emphasized. We also included prepubertal patients in our analysis. This considers the fact that STS are common in children and young adults. In addition, we focused on the effect of chemotherapy and excluded other gonadotoxic therapies such as radiotherapy or immunotherapies. By using the outcome parameter "suspected infertility," we have considered various clinically relevant parameters and thus the heterogeneous data situation regarding fertility parameters in the existing studies in this field.

The weaknesses of our study must also be acknowledged. First, the exact pubertal status was not always known for all study participants. Second, the heterogeneity of the fertility parameters as well as the limited number of studies led us to use the broader outcome parameter "suspected infertility." Interestingly, one of the reviewed studies used this term.[25] Balcerek et al. also used the term in their work on fertility after treatment of leukemia and solid tumors.[27] They defined the criteria for suspected infertility as AMH levels below 0.1 ng/mL in females, follicle stimulating hormone levels above 10 IU/L, and inhibin B levels below 80 pg/mL or azoospermia in males. And third, due to the frequently missing information on the exact chemotherapy regimen and dose used, we were unable to differentiate further according to the regimen used, dose, or age.

The age structure of the included studies reflects that STS occurs frequently in children and young adults. Most cancer survivors were prepubertal at the time of diagnosis or treatment. The assessment of gonadal function appears to be possible in this age group using conventional parameters such as AMH and gonadotropin levels, provided that sufficient follow-up is carried out.[28] Follow-up was adequate in most studies with males being reassessed after the onset or after puberty. In those with females, the follow-up time line was insufficient. According to our data, the prepubertal situation does not appear to provide protection against gonadotoxicity. For example, all prepubertal males in the study by Kenney et al.[26] showed a severe restriction in the semen analysis in the sense of crypto- or azoospermia. This was also the case >5 years after gonadotoxic treatment, which postulates irreversible gonadal damage. In contrast to earlier data,[29] more recent studies[30–32] seem to show that prepubertal gonads are not protected but are more sensitive to gonadotoxic therapies, which supports our findings.

Assessment of treatment-related infertility in these cancers is challenging, as the gonadotoxic effects of their therapeutic interventions in STS have been less studied compared with more common cancers. The degree of gonadotoxicity depends on the specific therapeutic interventions used.[33] In early-stage disease, resection of the tumor is the treatment of choice, with or without neo- or adjuvant radiotherapy, dependent on the histological subtype and risk situation. Chemotherapy is usually applied for high-risk sarcomas, unresectable or R1-resected sarcomas, and advanced-stage disease.[7] Within the chemotherapy regimen, characteristics such as dosage and the choice of chemotherapeutic agents significantly influence the extent of gonadal damage.[33] Treatment for STS often involves polychemotherapy regimens with combinations containing alkylating agents, such as cyclophosphamide or ifosfamide, or anthracyclines, such as doxorubicin.[7] According to the ESMO guideline,[7] there is no formal evidence that alkylant-based polychemotherapy is superior to monochemotherapy with an anthracycline (doxorubicin) in terms of overall survival.

However, it may result in a better response and longer progression-free survival, which is why polychemotherapy is often used and may be a regimen of choice. For both these cytotoxic agents, a significant, dose-dependent gonadotoxicity has been demonstrated, which supports our results.[34–38] The included study by Kenney et al.[26] shows that no or only reversible fertility impairment is to be expected at a cyclophosphamide dose <7.5 g/m2. In contrast, all males with doses >25 mg/2 were azoospermic. Consistent with this, gonadotropins were frequently, but not always, elevated. Interestingly, all males showed normal testosterone levels, possibly explained by a lower chemosensitivity of the Leydig cells.[30] The specific individual gonadotoxic risk is sometimes difficult to quantify. In addition to various guidelines,[9,10,39] there are tools, such as the classification by Wallace et al. from 2005,[40] which help to assess the gonadotoxicity of chemotherapies and to counsel accordingly. The development of reliable calculation tools to assess the individual risk of gonadotoxicity, dependent on the therapy in question, but also taking into account patient- and disease-related factors, would be of significant benefit. This issue would require further investigation through targeted, large-scale prospective studies. One approach to reduce gonadotoxicity could be to lower the dose of chemotherapy. An ongoing study by Miyachi et al. is currently investigating the oncological safety of a dose reduction of cyclophosphamide and the effect on gonadotoxicity in rhabdomyosarcoma.[41]

Apart from the extent of gonadotoxicity, the question of reproductive outcomes in STS patients arises in clinical practice of counseling in fertility preservation. These are poorly described in the literature for STS. Accordingly, none of the studies included in our review considers outcomes related to pregnancy rates, risks of oncologic therapy for pregnancy and offspring. In accordance with most studies, chemotherapy, unlike radiotherapy,[42] does not appear to be associated with adverse pregnancy and offspring outcomes after cancer treatment,[43,44] The work of Green et al. in the Childhood Cancer Survivor Study examined the pregnancy outcomes of females who survived childhood cancer.[43] This included 480 females with STS. No increased late miscarriage or reduced live birth rate was found, regardless of whether alkylants or other chemotherapeutic agents had been used. After radiotherapy of the pelvis, however, there was an increased risk of low birth weight <2500 g. Pregnancy after chemotherapy

is therefore generally considered safe in survivors of STS, provided the oncological prognosis is good.[43,45]

In the individual case of counseling for fertility preservation, several questions remain unanswered. The effect of age on risk of infertility could not be evaluated due to limited data. Furthermore, additional radiotherapy or immunotherapy and patient-specific factors such as the existing internal or urological comorbidities can have a negative influence.[9] Also, the most important, what is the effect of new treatment protocols currently developed?

As the drugs used in interdisciplinary therapy concepts for STS, and in particular for rhabdomyosarcomas in children, have remained practically unchanged over the last few decades, the results of our study are very up-to-date and can be used as a reference for today's clinical routine. Nevertheless, progress in molecular genetics will enable us to investigate newer drugs with a different mechanism of action in the future and therefore intervening with gonadotoxicity and fertility.[46]

However, counseling on fertility preservation measures will remain an important part of oncological treatment, which is likely to stay gonadotoxic despite advances in cancer therapy. In fact, counseling will become increasingly challenging as personalized treatments make it more difficult to estimate the individual risk of infertility. Large-scale studies such as the FertiTOX project,[12] organized by FertiPROTEKT (www.fertiprotekt.com), which collect comprehensive data, are therefore an important step toward improving counseling and protecting the fertility of cancer patients.

Conclusions

In conclusion, our review shows that data on the gonadotoxicity of chemotherapy for STS are very limited. However, there are sufficient data to estimate a high risk of chemotherapy-induced infertility in pre- and postpubertal females and males. This underlines the importance of comprehensive counseling and fertility protection for this complex tumor entity. Further research is needed to increase the quantity and quality of data and to assess the gonadotoxicity of new treatment protocols.

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Authors' Contributions

M.v.W. and S.W. designed the systematic review. T.K. set up the templates for literature search. Literature was searched by A.R., F.P., and M.S. Data analysis was performed by M.S. Oncological advice was given by A.K. The article was written by M.S. All authors revised the final article.

Author Disclosure Statement

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Supplementary Material

Supplementary Data S1

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