

## **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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### **Study question**

What is the gonadotoxicity of soft tissue sarcoma chemotherapies to better counsel females and males about the risk of infertility?

### **Summary answer**

Limited data about the gonadotoxicity indicate a rather high risk with an average suspected infertility in females of 71% and in males of 54%.

### **What is known already**

There is increasing awareness of the need to counsel young female and male cancer patients about the gonadotoxicity of chemotherapies and the risk of infertility. In addition, fertility preservation measures are offered in most countries.

However, our knowledge of the gonadotoxicity of most cancer diseases and chemotherapies is still limited making it difficult to indicate fertility preservation measures. Soft tissue and mesothelial cancer are such a types of cancer for which data is very poor. The gonadotoxicity and risk of infertility of soft tissue and mesothelial cancer has not yet been systematically reviewed.

### **Study design, size, duration**

This review is part of the FertiTOX project ([www.fertitox.com](http://www.fertitox.com)) which aims to close the gap of data regarding gonadotoxicity of cancer therapies to enable more accurate counselling regarding fertility preservation. A systematic literature search considering papers on gonadotoxicity of treatment of soft tissue sarcoma and mesothelial cancer was performed. A total of 2818 records were identified for abstract screening. The review was performed from December 2022 until October 2023.

### **Participants/materials, setting, methods**

A literature search of papers published in the databases of MEDLINE, Embase, and Cochrane Library since 2000 was performed. Only females and males without metastases or recurrent disease were considered. Due to limited infertility data the outcome parameter "Suspected infertility" was defined based on reported low ovarian reserve parameters, low inhibin B, high gonadotropin concentration, gonadal dysfunction, amenorrhea, oligomenorrhea, azoospermia or oligozoospermia.

### **Main results and the role of chance**

The database search yielded a total of 2818 abstracts, 136 of which were included in the full-text analysis.

Of these, 7 studies, each on soft tissue sarcomas, could be included in the review. Studies on mesothelial cancer could not be identified. Two of the 7 soft tissue sarcoma studies were retrospective and 5 were prospective. Of the 7 studies, 3 provided data on women, 3 on men and 1 on both genders. A total of 28 women and 50 men, a total of 78, were included. The pubertal status could not be determined for all patients. Suspected infertility was found in 20

of 28 (71.4%, range 0-100%) of females (4 studies) and in 27 of 50 (54%, range 34.8-100%) of males (4 studies) soft tissue sarcoma patients.

**Limitations, reasons for caution**

The weakness is the inclusion of prepubertal and pubertal females and males, and the unknown pubertal status in some cases. A further weakness is the heterogenous spectrum of infertility markers and the limited number of studies which required to define for the analysis the rather vague outcome parameter “suspected infertility”.

**Wider implications of the findings**

Our data suggest a high risk of infertility due to chemotherapies in soft tissue sarcomas. This appears to be more pronounced in females than in males, although precise information cannot be given due to limited data. However, even though the study emphasizes the importance to consider fertility preservation measures.

**Study funding/competing interest(s)**

No conflicts of interest to declare.

**Trial registration number**

PROSPERO (Registry number CRD42023385402)