EDITORIAL

Fertility in Survivors of Childhood Cancer

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Editorial to accompany the article "Suspected Infertility After Treatment for Leukemia and Solid Tumors in Childhood and Adolescence" by Magdalena Balcerek and Simone Reinmuth et al. in this issue of *Deutsches Ärzteblatt International*

The advances in treatment in recent decades have resulted in a continuous increase in the long-term survival probability after cancer in childhood (currently around 80% in Germany [www.kinderkrebsregister.de]). Many former patients want to start a family.

Staff members at the German Childhood Cancer Registry (GCCR) occasionally have personal contact with former patients (1). Anecdotally, we observe that the desire to have children plays an important part in their lives. It seems that concern about the health of any children they might have outweighs the question of their own fertility. Plainly, the wish for children is not always put into practice.

Registry studies from Italy and Finland, covering 6000 and 26 000 patients respectively, concur in showing that survivors of childhood cancer become parents around half as often as members of control groups (2, 3). Both studies report a particularly high rate of childlessness for brain tumor survivors. It can be assumed that the figures for Germany are similar.

The validity of epidemiological studies

When dealing with epidemiological studies, especially those on topics as sensitive as this, one must always consider the influence of the methods on the findings. Registry studies offer complete coverage of a population with hardly any selection. However, they lack detailed information on the individual members of the study group, such as the reasons for childlessness. On technical and data protection grounds, studies like those by Pivetta et al. (2) and Madanat et al. (3) could not be carried out in Germany.

Inversely, surveys or investigations of volunteers yield detailed information, but only from those who are willing and able to take part. The tendency is for the participants to be principally persons who have already delved into the topic concerned, e.g., cancer survivors whose wish for children has not been fulfilled. This applies also to the interpretation of the data from the largest study of survivors of childhood cancer anywhere in the world, the Childhood Cancer Survivor Study (CCSS) in the USA. Of the approximately 20 000 eligible former patients, around 6000 men and 5000 women were surveyed. Over 6000 of the 20 000 patients did not participate in the study because they chose not to do so or could not be located (4, 5). The CCSS control group comprises the participants' siblings, around 80% of whom agreed to take part. The

modus operandi largely excludes survivors with cognitive deficits and constitutes social selection.

Balcerek, Reinmuth et al. (6) surveyed former patients registered in the German Childhood Cancer Registry. The German Childhood Cancer Registry excludes some patients from any subsequent surveys because they or their parents have refused to allow data storage or survey participation. This applies only to a small number of survivors overall (<5%), but a somewhat higher proportion of brain tumor survivors (6%).

In this issue of *Deutsches Ärzteblatt International*, Balcerek, Reinmuth et al. present the findings of two studies on this subject in Germany: a survey of former patients in the German Childhood Cancer Registry and a study of the results of hormone testing and sperm analysis in Berlin (6). Around 60% of the circa 4500 persons contacted consented to take part in the former, while only around 20% of the approximately 750 persons interviewed agreed to participate in the smaller Berlin study, which involved an investigation.

A response rate of 60% is on the high side of normal, but the usual social selection has to be assumed. A rate of 20% points to a considerable degree of self-selection; the patients presumably had a well-founded interest in the fertility testing that was offered. This underlines how important it is to describe the recruitment of patients for such a study precisely and to state clearly for which subgroups the conclusions may be valid and to which they do not apply.

The rate of infertility in survivors

The principal risk factors for impairment of fertility in survivors of childhood cancer (7) are:

- Age at time of treatment
- Chemotherapy with alkylating agents
- Irradiation of the reproductive organs or the hypothalamus/hypophysis.

Not all former patients are affected by these risk factors, and not all those who are affected show signs of infertility. The authors of a recent study in the Netherlands contacted approximately 800 male survivors, 70% of whom agreed to be investigated. Around 30% of those examined displayed signs of impaired fertility (8). In another recent study from Norway, measurement of anti-muellerian hormone levels identified potential problems with fertility in 20% of the around 60 women examined (9). The German publication in this issue cites further studies which conclude that up

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to one third of survivors of childhood cancer are infertile (6).

The authors of the German report describe a much lower rate of pregnancies in their study population than in the corresponding age segment of the general population (without quantitative data). The individual data on amenorrhea, fertility tests, unsuccessful attempts to conceive, etc. do not permit any conclusions as to what proportion of the participants can be classified as possibly infertile. However, it seems to be less than 30% of all responders.

In both the small, unrepresentative group of patients who accepted the offer of fertility testing in the Berlin hormone and sperm analysis study and the group of participants in the nationwide registry-based study who reported a previous fertility test, the rate was under 25%.

Conclusions

Early counseling of adolescent cancer patients and the parents of children with cancer seems advisable, even though it unavoidably takes place shortly after diagnosis and thus at a time of severe stress. For those involved, however, who see cancer first and foremost as a threat to life, the very fact that consequences of treatment in the distant future are discussed at all represents a message of hope (10). The content of the counseling should be tailored to the severity of the risk to fertility, which depends both on the disease itself and on the planned treatment. It must be remembered that not all fertility-preserving measures come into question for all patients, and that the costs of removal and storage of sperm, oocytes, or tissue are predominantly not covered by German providers of statutory health insurance.

In addition to the patients whose childlessness is a consequence of their illness or its treatment, there are those who decide not to become parents on psychosocial grounds, e.g., because they worry about possible health risks for the children. Since such concerns are usually unfounded, corresponding counseling of adult survivors who want children seems advisable.

Conflict of interest statement

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