Long-term effects on fertility after treatment of childhood, adolescents & young adults' central nervous system cancer: A systematic review and meta-analysis

Short title: Fertility after CNS cancer treatment

Janna Pape[1*], Tanya Gudzheva[2*], Beeler Danijela[3*], Susanna Weidlinger[4], Angela Vidal[5], Rhoikos Furtwängler[6], Tanya Karrer[7], Michael von Wolff[8]

[1]Division of Gynecological Endocrinology and Reproductive Medicine, University Women´s Hospital, Inselspital Bern, University of Bern, Switzerland. E-Mail: janna.pape@insel.ch
[2]Division of Gynecological Endocrinology and Reproductive Medicine, University Women´s Hospital, Inselspital Bern, University of Bern, Switzerland. E-Mail: tanya.gudzheva@insel.ch
[3]Division of Gynecological Endocrinology and Reproductive Medicine, University Women´s Hospital, Inselspital Bern, University of Bern, Switzerland. E-Mail: danijela.beeler@insel.ch
[4]Division of Gynecological Endocrinology and Reproductive Medicine, University Women´s Hospital, Inselspital Bern, University of Bern, Switzerland. E-Mail: susanna.weidlinger@insel.ch
[5]Division of Gynecological Endocrinology and Reproductive Medicine, University Women´s Hospital, Inselspital Bern, University of Bern, Switzerland. E-Mail: angela.vidal@insel.ch
[6]Division of Pediatric Hematology and Oncology, Dep. Of Pediatrics, Inselspital, University of Bern, Switzerland, Rhoikos.furtwaengler@insel.ch
[7]Medical Library, University Library Bern, University of Bern, Switzerland. E-Mail: tanya.karrer@unibe.ch
[8]Division of Gynecological Endocrinology and Reproductive Medicine, University Women´s Hospital, Inselspital Bern, University of Bern, Switzerland. E-Mail: Michael.vonWolff@insel.ch
*contributed equally

ABSTRACT

Background: Central nervous system (CNS) cancers represents the most common group of solid tumours in childhood & young adults. Due to treatment advancements in recent decades, with increasing survival rates, disorders of the hypothalamus-pituitary-axis (HPG) have become increasingly relevant for patients' future fertility plans. Most guidelines recommend that physicians should counsel their patients about fertility prognosis before initiating gonadotoxic therapy. However, for counselling on fertility preservation measures only expected risk of infertility due to gonadal toxicity is relevant which has not yet been systematically reviewed.

Objectives: To evaluate the potential impact of CNS cancer therapies on gonadal function to enable more accurate counselling regarding fertility preservation before the onset of oncological therapy.

Materials and Methods: A systematic literature search was performed in Medline, Embase and Cochrane in December 2022, and last updated in January 2024. The systematic review included studies of patients with a mean age of 12 years who had undergone treatment for all types of malignant CNS cancer. Studies with patients who had undergone stem cell or ovarian tissue transplantation were excluded from the meta-analysis. The outcomes were defined as clinically relevant gonadal toxicity, indicated by basal LH or FSH levels above the upper limit of the reference range and/or low anti-Mullerian hormone (AMH) levels in women or low inhibin B in men, and/or azoo-/oligozoospermia, as well as preserved fertility, indicated by no signs of gonadal toxicity including primary/secondary amenorrhea, no central/primary/secondary hypogonadism, or panhypopituitarism.

Results: The qualitative analysis included 28 studies with a total of 4303 patients after CNS cancer. Treatment comprised combinations of surgery, standard protocols of chemotherapy and cranial or craniospinal radiotherapy in different dosages. Gonadal toxicity was evaluated in 14 studies. All other studies focused on general effects on the HPG axis. After excluding studies involving patients who underwent stem cell transplantation and ovarian tissue transplantation, 21 studies were included in the quantitative synthesis. The overall pooled prevalence of gonadal toxicity was found to be 14% (8-23%, 95% CI). Preserved fertility was present in 80% (95% CI, 71-86%) of the patients with a trend towards higher prevalence after at least five years following treatment (90%, 95% CI: 76-96%).

Conclusion: This initial meta-analysis provides a basis for fertility counselling on the overall gonadal toxicity and preserved fertility after diverse CNS cancer treatments. Due to the high heterogeneity of the study population, it is not possible to provide an exact estimation of the fertility prognosis. However, the data indicate that overall gonadal toxicity is low. Therefore, in prepubertal patients who are under high clinical treatment pressure, it seems justifiable to forego fertility preservation measures. However, for postpubertal patients, fertility preservation measures are still recommended due to the uncertainty of subsequent therapy and the lack of large longitudinal data on individual treatment effects.