Impact on Fertility Outcomes in Survivors after Hematopoietic Stem Cell Transplantation for Benign and Malignant Hematologic Disorders: A systematic review and meta-analysis

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STUDY QUESTION: What is the prevalence of infertility after hematopoietic stem cell transplantation (HSCT) in females and males up to the age of 1 year?

SUMMARY ANSWER : The overall prevalence of infertility (95% CI) in women treated with HSTC is 64% (0.58-0.70) and in men 39% (0.31-0.47).

WHAT IS KNOWN ALREADY:

HSCT is a well-established treatment that has significantly increased survival in haematological malignancies and benign diseases since its introduction in the 1980s. The use of high-dose chemotherapy and radiotherapy, myeloablative conditioning, combined with HSCT exposes serious long-term complications, including gonadal dysfunction and infertility. The risk of ovarian and testicular damage seems to be very high. Therefore, the European Society for Blood and Marrow Transplantation (EBMT) had recommended in 2015 to consider fertility preservation measures in children and adolescents requiring HSCT. However, the data on which this recommendation was based was limited and heterogeneous. A meta-analysis addressing this topic and analyzing the risk of infertility of HSCT has not yet been performed.

STUDY DESIGN, SIZE, DURATION : The systematic review and meta-analysis is part of the FertiTOX project (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 was conducted in Medline, Embase and Cochrane in November 2023, considering papers published since 2000.

PARTICIPANTS/MATERIALS, SETTING, METHODS : A total of 1632 records were identified for abstract screening. Only females and males without recurrent disease and follow up of more than one year were considered. For the systematic review, 68 studies fulfilled the criteria. For the meta-analysis, studies with cohorts < 10 patients were excluded. Infertility was defined in females as very low AMH, hypergonadotropic hypogonadism, amenorrhoea and/or need for hormone replacement therapy and in males as low inhibin B and/or azoospermia.

MAIN RESULTS AND THE ROLE OF CHANCE : In total, 68 out of 1632 studies were included in the final analysis. Malignant diseases were mainly acute myeloid / lymphoblastic leukemia, chronic myeloid leukemia/ lymphocytic leukemia and non-hodgkin's and hodgkin's lymphoma. Benign diseases were sickle cell disease, Fanconi anaemia, and β-thalassemia major. In the meta-analysis, 56 studies were included, comprising 1853 female malignant cases, 241 female benign cases, 1871 male malignant cases, and 226 male benign cases. The analysis, employing a random-effects model for estimating prevalence and its 95% confidence interval, revealed that the overall pooled prevalence of infertility exceeded 30% in all groups. The prevalence of infertility was highest in female malignant cases (65%, 95% CI: 0.58-0.71). In women with benign diseases it was 61% (95% CI: 0.48-0.73). In males with malignant diseases it reached 41% (95% CI: 0.32 to 0.51) and with benign diseases 31% (95% CI: 0.19 to 0.46). Heterogeneity of data was high as shown by female as shown by the malignant cases of (I^2 = 83%, $p < 0.01$) and benign cases of (I^2 = 65%, $p < 0.01$) in women and the malignant cases of (I^2 = 91%, $p < 0.01$) and benign cases of (I^2 = 74%, $p < 0.01$) in males.

LIMITATIONS, REASONS FOR CAUTION:

The heterogeneity of the included studies due to treatment variations and diverse characteristics of the study populations with large age ranges, did not allow further subgroup analyses. Thus, an individual and reliable fertility prognosis is still difficult to give.

WIDER IMPLICATIONS OF THE FINDINGS:

The results of this meta-analysis support the clinical necessity of fertility preservation counselling in females and males undergoing HSCT treatment. Further prospective studies addressing the individual impact of the HSCT treatment on gonadal function are needed.

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TRIAL REGISTRATION NUMBER : The study protocol was registered at the international Prospective Register of Systematic Reviews, PROSPERO (Registry number CRD42023486928).