Fertility preservation counseling: A novel user-friendly tool for evaluating the risk of acute ovarian failure in childhood cancer survivors

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Guidelines recommend that appropriate information about the effects of cancer treatment on ovarian function and future fertility be provided to all paediatric patients and their families¹,²

Although fertility counselling in children and adolescents is more complex than in adults, the risk of acute ovarian failure (AOF), defined as permanent discontinuation of menstruation within 5 years or primary amenorrhea, is also a major concern in this population as it dramatically impacts long-term quality of life. The evaluation of this risk is often difficult in young patients and prospective studies are scarce. The Childhood Cancer Survivor Study
(CCSS) provided important data leading to estimates that the overall prevalence of AOF is 6% in childhood cancer survivors. 3 The occurrence of this side-effect is highly variable according to the type and dose of treatment, the disease, and the age of the child at diagnosis. Children and adolescents treated with high doses of alkylating agents, hematopoietic stem cell transplantation (HSCT), or pelvic irradiation are considered to be at high risk (>80%) of future subfertility. 4 Although risk factors have been previously identified, access to accurate and easy predictive models for predicting AOF risk remains a unmet need, impacting the decision to offer fertility preservation procedures.

In their article in the Lancet Oncology, Rebecca A. Clark and colleagues provide a user-friendly and rigorous tool that is available online for the prediction of the risk of AOF in children treated for cancer. The key strength of this approach is the robustness of the data and of the methodology. In order to implement and validate the model, two large cohorts from CCSS and the St Jude Lifetime (SJLIFE) study (5886 and 875 eligible cancer survivors diagnosed before age 21, respectively), were retrospectively analyzed based on several parameters including age at diagnosis and menarche, type of cancer, chemotherapy exposure, cyclophosphamide equivalent dose (CED), HSCT, ovarian radiation dose received and prescribed. Ovarian status assessments were based mainly on menstruation history to define AOF and non-AOF patients. This model was effective for stratification of each patient into one of the four defined AOF risk groups (low, medium-low, medium, and high). Although the methodology relied on retrospective data on self-reported menstrual history, hormone levels were available in the SJLIFE cohort used for external validation. The use of oral contraceptive pills within 5 years of diagnosis could be considered as a potential source of bias but this concerned less than 1.5% of the CCSS population. The model performed well when validated externally in the SJLIFE cohort.
However, the model, designed to provide an evaluation of the risk of AOF or failure to achieve menarche at the age of 18 years, may underestimate the long-term risk of ovarian failure, leading to false reassuring counseling. Previous studies have demonstrated that childhood cancer survivors who have normal menstruation five years after diagnosis have a 13-times increased risk of developing PM. After 30 years of age, female cancer survivors from the CCSS cohort experienced an additional decrease in pregnancy likelihood compared to their siblings. Considering the delay in childbearing currently observed in many countries, long-term effects on fertility should be taken into account during counselling. Therefore, it would be important in the future to validate the model by including long-term follow-up. The authors encourage the users to apply the tool prospectively and publish their data, but multicentric studies would be wise to provide long-term reproductive outcomes on large cohorts, especially for patients stratified in the medium- and low-risk groups for whom fertility preservation is currently not recommended.

As fertility preservation programs became more accessible, a tempting approach would be to offer fertility preservation procedures to all children, irrespective of the AOF risk. However, this attitude raises serious ethical concern as the large majority of them will probably be fertile in adulthood and will not need further fertility restoration procedures. Overestimation of AOF risk can lead to unnecessary invasive procedures. Moreover, data on success rates of fertility preservation methods in children and adolescents remain very scarce, even for established procedures such as oocyte cryopreservation. The only available fertility preservation option in prepubertal girls is the cryopreservation of ovarian tissue, which is still designated as experimental. Of more than 1000 patients who underwent the procedure before age 21 worldwide, only 18 women have undergone ovarian tissue auto-transplantation to restore their ovarian function up to this time. Conversely, underestimation of the risk of ovarian failure may
lead to not offering fertility preservation in children with potential dramatic consequences to their future quality of life. Therefore, clinicians urgently need to have access to such user-friendly tools as the one designed by Rebecca A. Clark and colleagues, in order to help them make appropriate decisions with a real benefit for patients.

By providing accurate information regarding the risk of AOF through an available web application, Rebecca A. Clark and her colleagues will significantly improve counselling regarding fertility preservation in children and adolescents at the time of diagnosis. This could also represent a useful tool for future clinical research projects aiming to evaluate the effectiveness and the rationale for fertility preservation procedure in children.

References
