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Fertility preservation counselling for childhood cancer survivors

Guidelines recommend that appropriate information about the effects of cancer treatment on ovarian function and future fertility should be provided to all paediatric patients and their families.[1,2] Although fertility counselling in children and adolescents is more complex than in adults, the risk of acute ovarian failure, defined as permanent discontinuation of menstruation within 5 years of diagnosis or primary amenorrhoea, is a major concern in this population because it affects 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 acute ovarian failure in survivors of childhood cancer is 6%.[3] The occurrence of this side-effect varies greatly 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 drugs, haematopoietic stem-cell transplantation, or pelvic irradiation are considered to be at high risk (>80%) of future poor fertility.[4] Although risk factors have been previously identified, access to accurate and easy-to-use models for predicting future risk of acute ovarian failure remains an unmet need, affecting the decision of whether or not to offer fertility preservation procedures to children and adolescents with cancer.

In their Article in *The Lancet Oncology*, Rebecca A Clark and colleagues[5] provide a user-friendly and rigorous tool that is available online for the prediction of the risk of acute ovarian failure in children treated for cancer. The key strength of this approach is the robustness of the data and the methods used. To implement and validate the model, the CCSS cohort (5886 eligible cancer survivors diagnosed before age 21 years) and the St Jude Lifetime (SJLIFE) study cohort (875 eligible 10-year cancer survivors), were analysed retrospectively on the basis of several parameters, including age at diagnosis and menarche, type of cancer, chemotherapy exposure, cyclophosphamide-equivalent dose, haematopoietic stem-cell transplantation, and prescribed and received ovarian radiation dose. Ovarian status assessments were based mainly on menstruation history to define participants with and without acute ovarian failure. This model effectively stratified each patient into one of four defined risk groups for acute ovarian failure (low, medium-low, medium, and high). Although the methodological approach relied on retrospective data on self-reported menstrual history, hormone concentrations were available in the SJLIFE cohort that was 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 factor applied to 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 acute ovarian failure or not having menarche by the age of 18 years, might underestimate the long-term risk of ovarian failure, leading to counselling that is falsely reassuring. Previous studies have shown that childhood cancer survivors who had had normal menstruation 5 years after diagnosis had a 13-times increased risk of developing premature menopause.[6] Beyond 30 years of age, female cancer survivors from the CCSS cohort had an additional decrease in pregnancy likelihood compared with their siblings.[7] Considering the delay in childbearing currently observed in many countries, long-term effects on fertility should be taken into account during counselling. Therefore, the model needs to be validated in the future by including long-term follow-up. The investigators encourage the users to apply the tool prospectively and publish their data, but multicentre studies should provide long-term reproductive outcomes from large cohorts, especially for patients stratified in the medium-risk and low-risk groups for whom fertility preservation is currently not recommended.

As fertility preservation programmes become more accessible, a tempting approach would be to offer fertility preservation procedures to all children, irrespective of their risk for acute ovarian failure. However, this approach raises serious ethical concerns as most children will probably be fertile in adulthood and will not need fertility restoration procedures. Overestimation of the risk of acute ovarian failure can

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lead to unnecessary invasive procedures. Moreover, data about success rates of fertility preservation methods in children and adolescents are very scarce, even for established procedures such as oocyte cryopreservation.[8] 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 worldwide who have had the procedure before the age of 21 years, only 18 women have had ovarian tissue autotransplantation to restore their ovarian function so far.[8] Conversely, underestimation of the risk of ovarian failure might lead to children not being offered fertility preservation, with potential major negative consequences to their future quality of life. Therefore, clinicians urgently need to have access to such user-friendly tools as the one designed by Clark and colleagues, to help them to make appropriate decisions that could have a real benefit for patients at the time of diagnosis. Their tool could also be useful for future clinical research projects aiming to evaluate the effectiveness and the rationale for fertility preservation procedures in children.

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