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Long-term follow up to assess criteria for ovarian tissue cryopreservation for fertility preservation in young women and girls with cancer

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Study question:
Do the Edinburgh selection criteria correctly identify females, diagnosed with cancer under 18 years old, at high risk of future premature ovarian insufficiency (POI)?

Summary answer:
Patient assessment using these criteria accurately identifies those at risk of POI. Ovarian tissue cryopreservation with future transplantation can be offered, providing future fertility options.

What is known already:
Cancer treatments can be gonadotoxic and future fertility and reproductive health should be considered at the time of diagnosis and treatment planning. Correct identification of patients at high risk allows appropriate discussion of fertility preservation with ovarian tissue cryopreservation (OTC) and future transplantation. The Edinburgh selection criteria have been proposed as a tool to identify those patients at high risk.

However, the surgical procedure is not without risk and reproductive outcomes remain uncertain in girls. Therefore, long-term follow up of reproductive function is crucial to ensure that this treatment strategy is offered appropriately.**Study design, size, duration:**
All females diagnosed with cancer less than 18 years old, in South East Scotland, between 01/01/96 and 30/10/20 were included. They were assessed using the Edinburgh selection criteria and offered OTC, if appropriate. Ongoing long-term follow up of reproductive outcomes has been undertaken for the whole patient cohort to detect those who develop POI.

Participants/materials, setting, methods:
A total of 639 eligible patients were identified from the Cancer registry and their electronic records reviewed. Reproductive function was assessed by the presence of menstruation, pregnancy, hormonal measurements, evidence of puberty or diagnosis of POI. Patients on hormonal contraception (other than for the treatment of POI) were considered unsuitable for analysis.

Data were analysed using the Kaplan Meier method, with POI as the event, and the Cox proportional hazards model to calculate hazard ratios.**Main results and the role of chance:**
Of the 639 patients diagnosed with cancer during the study period, those deceased before age 12 years old (n=73) or under 12 years old (n=134) at the date of analysis were excluded; also excluding those on hormonal contraception (n=9) gave a study population of 423.

Data were analysed including those with unknown reproductive outcomes (n=143), assuming they did not have POI. A subgroup analysis excluding these patients was also performed.

Mean age at diagnosis and analysis was 8.8 years and 22.5 years respectively.

OTC was offered to 37 patients, 26 of whom underwent the procedure. Nine patients developed POI (24.3%). Of the 386 not offered OTC, 11 developed POI (2.85%). The hazard ratio for developing POI was 8.8 (CI 3.6-21).

Excluding the patients with unknown outcomes (n=143) left a study population of 280. Within this group, 9 of 29 offered OTC developed POI (31.0%) versus 11 of 251 not offered OTC (4.4%); hazard ratio 8.2 (CI 3.4-20).

In the group offered OTC, all cases of POI developed after the primary treatment. In those not offered OTC, POI developed after secondary treatment for disease relapse in 5 patients (45.5%).**Limitations, reasons for caution:**
A significant number of patients had unknown reproductive outcomes; this is likely to reflect a lack of recording of normal menstrual function in oncology/haematology clinics but may have biased the analysis. The duration of follow up is also short for some patients, highlighting the need for further follow up.

Wider implications of the findings:
The overall prevalence of POI after childhood cancer is low, but the Edinburgh selection criteria are a robust tool for selecting those at high risk at the time of diagnosis, who can be offered OTC. However, many patients

had incomplete information on current reproductive status, which should be assessed routinely.

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