

Fertility preservation utilizing controlled ovarian hyperstimulation and oocyte cryopreservation in a premenarcheal female with myelodysplastic syndrome

Advances in cancer treatment have made childhood cancer a curable disease in up to 75% of patients. However, chemotherapy and radiotherapy regimens are still associated with an important degree of gonadotoxicity. Data from the United States Childhood Cancer Survivor Study (CCSS) demonstrate an increased risk for acute ovarian failure, premature menopause, and reduced fertility in a large series of 5-year childhood cancer survivors (1) and indicate that prepubertal ovaries are also vulnerable to the gonadotoxic effects of cancer treatments.

The case report by Reichman et al. describes a successful ovarian stimulation and oocyte retrieval in a premenarcheal girl (2). It illustrates the potential to reduce the minimal age for ovarian stimulation and apply this method of fertility preservation in much younger age groups. For young girls, this novel approach may represent a promising additional tool to preserve fertility as an alternative for ovarian cortex freezing.

However, we should be aware of the possible risks associated with this approach. The authors rightfully underscore the risk for ovarian hyperstimulation syndrome (OHSS) in this patient population. The risk of OHSS can only be eliminated by the replacement of hCG to trigger final oocyte maturation by a GnRH agonist. Because the efficiency of GnRH agonist triggering has not been assessed in premenarcheal girls—who have an immature hypothalamic–pituitary–gonadal axis—reduced-dose hCG triggering could be considered as a safe alternative.

Careful selection of the gonadotropin stimulation dose is mandatory but hard to implement before menarche, because routinely available predictors of ovarian response, such as anti-Müllerian hormone (AMH) and antral follicle count, have not been validated in this patient population. In prepubertal girls, follicle growth up to the early antral stage is rare. Hence, ovarian stimulation using conventional methods is unlikely to yield oocytes in the vast majority of prepubertal girls. AMH is produced by early growing follicles at all stages up to the early antral stage, but it is unknown which class of growing follicles is the strongest contributor to circulating AMH concentrations. Therefore, AMH may not be a useful parameter to select prepubertal girls who would be likely to respond to ovarian stimulation.

The patient presented in the case report had a Tanner stage 3 breast development. At present, ovarian response to exogenous gonadotropins is undefined in children at earlier stages of puberty.

Generally, the number of mature oocytes that can be obtained after one cycle of ovarian stimulation limits oocyte cryopreservation. Therefore, we'll have to walk the thin line between careful stimulation and offering the patient a maximal number of oocytes for freezing.

Introducing ovarian stimulation to this group of patients does not rule out the possibility of a combined approach in

conjunction with ovarian cortex freezing. Ovarian tissue cryopreservation has long been considered the only option for prepubertal girls. Its main advantages are the minimal delay of the onset of cancer treatment and the possibility of spontaneous and repeated conception after autologous transplantation of ovarian tissue. However, this approach requires surgical procedures and may hold a risk of malignant cell contamination of the graft, with reintroduction of the disease.

Freezing or vitrification of ovarian cortex is quite successful at preserving a large number of primordial and primary follicles. However, many follicles are lost because of ischemic damage after transplantation. Moreover, assisted reproduction in women with frozen-thawed ovarian tissue appears to be associated with a relatively poor outcome, possibly reflecting a reduced follicular selection (3).

Ideally, future developments should make the need for ovarian tissue transplantation redundant. Advances in *in vitro* follicle growth performed on frozen-thawed ovarian tissue may be of particular interest to these young girls. These promising developments may well culminate in routine practice within their reproductive life span as these girls envisage motherhood only within 10 to 20 years' time. A recent study by Anderson et al. (4) demonstrated that human ovarian follicles can be activated to grow *in vitro* and can develop to the large, secondary stage. However, the findings from this study suggest that prepubertal girls represent a particular challenge: the authors found a high prevalence of abnormal oocytes and slow growth of follicles in the youngest girls, which led them to suggest that the techniques for *in vitro* culture in adults and older girls may not be suitable for prepubertal girls. These findings inevitably raise concern with regard to the quality of oocytes retrieved at prepubertal age, not only from the ovarian cortex but potentially also after ovarian stimulation.

Oocyte *in vitro* maturation (IVM) could be offered as another method to recover and store oocytes in prepubertal girls. Preovulatory antral follicles contain germinal vesicle-stage oocytes that do not survive cortex thawing. The potential of ovariectomy can be enhanced by follicular aspiration of these immature oocytes or by collecting oocytes from the dissected ovarian tissue before cryopreservation (5). These immature oocytes can then be successfully matured *in vitro*, followed by vitrification. This approach can be performed irrespective of the menstrual cycle and has also been performed in prepubertal girls.

In view of the increased survival after childhood cancer, this report offers a potentially promising alternative to ovarian tissue freezing. However, one swallow doesn't make a summer. Future case reports and series will undoubtedly follow and will enable us to evaluate the prospects of this approach. Eventually, it will probably take another decade before we can experience the birth of the first healthy child from oocytes retrieved at a prepubertal age.

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