haematologica
Journal of the Ferrata Storti Foundation

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Received: September 2, 2025.
Accepted: September 18, 2025.

Citation: Avraham Frisch. The sobering reality of fertility preservation in young female patients with acute leukemia.
Haematologica. 2025 Sept 25. doi: 10.3324/haematol.2025.288538 [Epub ahead of print]

The sobering reality of fertility preservation in young female patients with acute leukemia

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Declaration of Interests:

The author declares no competing interests.

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"Rachel envied her sister, and said unto Jacob, “Give me children, or else I die." (Genesis 30:1)

The desire of parenthood is deeply embedded in humans, with religious, cultural and psychological elements. Allogeneic bone marrow transplantation (alloSCT), which is the best post-remission therapy for patients with acute leukemia exhibiting high-risk genetics or with suboptimal response to initial treatment, is likely to result in ovarian failure among female survivors[1], particularly if preceded by myeloablative conditioning[2]. There is no standard procedure for fertility preservation in females with acute leukemia. Ovarian protection during chemotherapy with gonadotropin-releasing hormone agonists has not been proven to be beneficial in patients with hematologic malignancies[3], while other promising hormonal therapies, such as müllerian inhibiting substance, are at a pre-clinical stage of research. The cryopreservation of oocytes, which might be the best option for post-pubertal patients with cancer, often requires several weeks for ovarian stimulation and oocyte retrieval[4] whereas the treatment in acute leukemia cannot be delayed for so long in most cases. Furthermore, the coagulopathy that accompanies the diagnosis of acute leukemia, as well as the attendant neutropenia, hamper the safety of this method. Delaying and Implementing oocyte retrieval after achieving remission, where a delay in treatment might be possible and the coagulopathy and neutropenia had already been resolved, is discouraged, as the amount of oocytes retrieved is low[5], and there is a theoretic risk for DNA damage and aneuploidy, at least in animal models[6]. For pre-pubertal patients with leukemia, and for patients in whom the treatment cannot be delayed, the only realistic option is ovarian tissue cryopreservation (OTC) after achieving remission followed by ovarian tissue auto-transplantation (OTT) when ovarian failure is documented and a pregnancy is desired. Prior studies suggeste that chemotherapy exposure prior to OTC does not reduce the probability to conceive[7]. Moreover, the OTT leads to high rates of restoration of ovarian endocrine function. However, a concern was previously raised regarding the re-introduction of leukemic cells upon transplanting the ovarian tissue[8]. The modalities available for fertility preservation in females with acute leukemia are illustrated in figure 1

In this issue, Chevillon and colleagues report the largest cohort of 13 female survivors of alloSCT who successfully underwent OTT in order to be able to conceive, all without other contraindications for pregnancy and in long-term remission after transplantation[9]. This cohort represents the tip of the iceberg of candidates for alloSCT who are referred to OTC, and yet, the results are very disappointing, with only 3 women who became pregnant and only 1 live birth at the risk of a presumed OTT-originated relapse. The work by Chevillon et al raises the issue of the true overall effectiveness of OTC in patients planned to undergo an alloSCT for acute leukemia. The 5-year survival post alloSCT is only 40-70%, and as many as 30-40% of survivors will experience chronic extensive graft-versus-host disease (GVHD) which precludes pregnancy. Even allowing for recent advances in GVHD prevention and management (e.g. post-transplant cyclophosphamide, roxulitinib, belomosudil), the rates of chronic extensive GVHD is 15-20%[10]. Many of the survivors will suffer from sexual dysfunction or be left unemployed and thus unable to support a child. Indeed, three of the women in this paper had planned for a pregnancy and therefore underwent OTT, but later declined this for non-medical issues. This emphasizes the socio-economic burden of alloSCT in survivors. Moreover, the concept of requiring the eradication of measurable minimal residual disease (MRD) prior to transplant [11], has only been prospectively established in B-ALL with blinatumomab. Thus, many patients with AML at higher risk are likely to be with minimal residual disease at the time of alloSCT and, as a consequence, presumably also in the ovarian tissue[12]. In such patients, OTT would be contraindicated.

In addition to the cost-effectiveness, the safety of OTT is a matter of debate, as the ability to truly rule out the presence of leukemic cells in ovarian tissue is limited. The best MRD standard testing are at a sensitivity of 10^{-5}, which might not be sufficient. Indeed, the patient who relapsed in the current paper, had unmeasurable MRD in the ovarian tissue, and yet experienced relapse, although it remains unproven whether the relapse occurred from occult leukemic cells in the ovarian tissue. Furthermore, many of the patients with genetically defined high-risk AML, and some of the ALL, patients have no molecular marker for qPCR monitoring. These patients are often monitored with flow cytometry at a lower sensitivity of 10^{-3}-10^{-4} .

In summary, Chevillon et al are challenging the practice of fertility preservation by OTC followed by OTT in alloSCT candidates both by the questionable safety and the low efficacy of the procedure. Given the lack of alternatives for fertility preservation in these patients, future improvement in GVHD treatment, potential post alloSCT maintenance therapies (e.g. menin inhibitors in AML) as well as more precise methods for MRD detection, such as NGS based patient specific IGH/TCR testing and customized qPCR for AML with unique translocations might enable an enhanced risk-benefit assessment. Since biblical times, the desire of women to attain motherhood goes far beyond the simple rationale. As physicians, we must be sensitive to this and not reflexly discourage all women who are determined to conceive. Given current knowledge, it is likely that OTT will continue to be offered to selected, determined women after full consideration of all risks.

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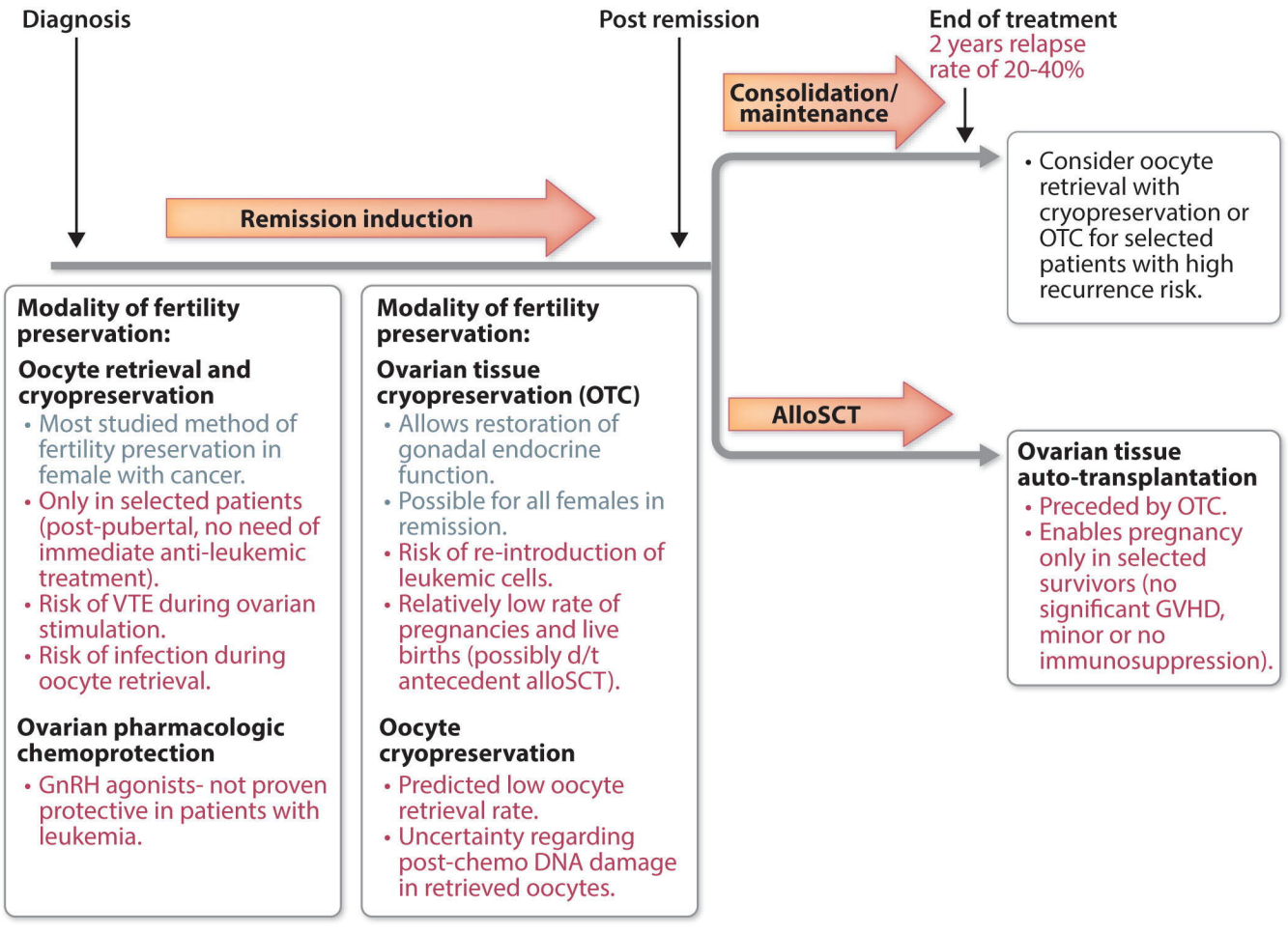
Figure 1. Timeline of various fertility preservation methods in female patients with acute leukemia.

In gray - advantage of modality. In red - disadvantage of modality.

Note that after completion of post-remission chemotherapy, spontaneous pregnancy is often possible as the risk of ovarian failure is <20%.


Diagnosis
Post remission
End of treatment
2 years relapse rate of 20-40%
Consolidation/ maintenance
Remission induction
• Consider oocyte retrieval with cryopreservation or OTC for selected patients with high recurrence risk.
Modality of fertility preservation:
Oocyte retrieval and cryopreservation
• Most studied method of fertility preservation in female with cancer.
• Only in selected patients (post-pubertal, no need of immediate anti-leukemic treatment).
• Risk of VTE during ovarian stimulation.
• Risk of infection during oocyte retrieval.
Ovarian pharmacologic chemoprotection
• GnRH agonists- not proven protective in patients with leukemia.
Modality of fertility preservation:
Ovarian tissue cryopreservation (OTC)
• Allows restoration of gonadal endocrine function.
• Possible for all females in remission.
• Risk of re-introduction of leukemic cells.
• Relatively low rate of pregnancies and live births (possibly d/t antecedent alloSCT).
Oocyte cryopreservation
• Predicted low oocyte retrieval rate.
• Uncertainty regarding post-chemo DNA damage in retrieved oocytes.
AlloSCT
Ovarian tissue auto-transplantation
• Preceded by OTC.
• Enables pregnancy only in selected survivors (no significant GVHD, minor or no immunosuppression).