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FERTILITY PRESERVATION

# Cryopreserved ovarian tissue autotransplantation in an acute myeloid leukaemia survivor following extensive minimal residual disease screening: first reported live birth in Europe

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## Abstract

**Purpose** We report successful autotransplantation of ovarian tissue in a sterile acute myeloid leukaemia survivor after comprehensive minimal residual disease (MRD) screening.

**Methods** At age 18, the patient underwent ovarian tissue cryopreservation while in complete remission prior to allogeneic stem cell transplantation. Premature ovarian failure and the wish to conceive led her to request transplantation of her cryopreserved ovarian tissue 12 years later. Extensive MRD screening of frozen-thawed biopsy specimens, including histology, immunohistochemistry, PCR and 6-month xenotransplantation to immunodeficient mice, was conducted before ovarian tissue transplantation (OTT).

**Results** Histology and immunohistochemistry (MPO, p53, CD4, CD45) of thawed ovarian fragments showed no malignant cell contamination. Nested RT-PCR (MLL::AF9) was negative and the mouse grafted with ovarian tissue showed no disease after 6 months. The xenografted tissue was analyzed again (histology, immunohistochemistry and RT-PCR) and showed no contamination. Laparoscopic transplantation to the patient restored ovarian function after 4 months. Modified natural cycle IVF resulted in pregnancy. At 29 weeks, the patient had preterm premature rupture of membranes and delivered a healthy boy at 34.5 weeks. Three years post-transplantation, the patient remains disease-free.

**Conclusions** Concerns about malignant cell contamination limit cryopreserved OTT in leukemia survivors. This is the first reported European live birth in an acute myeloid leukemia survivor following frozen-thawed OTT. Safe OTT was achieved by retrieving ovarian tissue during complete remission and conducting thorough screening before transplantation. Obstetrical risks in leukemia survivors who had total body irradiation should also be thoroughly discussed during decision making before attempting motherhood.

**Keywords** Fertility preservation · Leukaemia · Minimal residual disease · Ovarian tissue cryopreservation · Ovarian tissue transplantation

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## Introduction

With rising survival rates among young female cancer patients often assosiated with potential treatment-induced gonadotoxicity, fertility preservation has become an integral part of cancer care [1, 2]. Ovarian tissue cryopreservation (OTC) is currently the only established way of safeguarding fertility in prepubertal girls and subjects requiring urgent cancer treatment [1, 2]. This procedure, which involves laparoscopic tissue retrieval followed by freezing of ovarian cortex, does not delay cancer therapy. In survivors facing premature ovarian failure (POF), their thawed tissue can be grafted back to restore fertility and endocrine function [3]. There are nevertheless concerns about the risk of reseeding cancer cells in case of acute leukaemia, due to the presence of malignant cells in the bloodstream and hence also the ovaries [4–7].

For this reason, while acute leukaemia is a common indication for OTC [8–10], ovarian tissue transplantation (OTT) has not been widely performed in leukaemia survivors. This case report describes an acute myeloid leukaemia (AML) patient who, after OTC and thorough evaluation of her cryopreserved ovarian tissue for any malignant contamination or minimal residual disease (MRD), successfully underwent OTT, leading to a pregnancy and live birth. This is the first reported European live birth following OTT in an AML survivor.

## Case report

The case described here refers to a female patient diagnosed with AML (AML-M5, according to the WHO classification) in 2007 at 18 years of age. A disease-specific chromosomal translocation t [9, 11] (p21-22;q23) was identified in her lymphoblasts upon diagnosis, resulting in the MLL::AF9 fusion transcript. Induction therapy was initiated immediately in accordance with the AML-12 protocol of the EORTC, including daunorubicin, cytarabine and etoposide. The patient achieved complete remission after induction chemotherapy, and allogeneic stem cell transplantation was scheduled.

Given the severe gonadotoxic effects associated with a conditioning regimen comprising high-dose cyclophosphamide (120 mg/kg in 2 days) and fractionated total body irradiation (1375 cGy in 10 sessions), the patient was referred for fertility preservation before allogeneic stem cell transplantation. Laparoscopic unilateral (right) oophorectomy was performed in AZ Sint-Jan, Bruges, and the excised ovary was transported to Vrije Universiteit Brussel, Brussels, for cryopreservation. The ovary was transported as a whole in a sterile container containing NaCl 0.9% and placed on crushed, melting ice (0 °C) in an insulated box. Transport took 2h20min from surgery to arrival. Eleven tissue fragments (average size $0.9 \times 0.7 \times 1.5$ mm) were cryopreserved using a slow-freezing protocol. In November 2007, the patient underwent an allogenic stem cell transplantation from an HLA-identical sibling donor.

In 2019, 12 years after achieving complete remission from AML, the patient presented at our fertility unit requesting transplantation of her ovarian tissue. She had developed POF as a result of a myeloablative conditioning regimen. Having discontinued hormone replacement therapy (HRT), her gonadotropin levels indicated post-menopausal status (follicle stimulating hormone [FSH] > 50 IU/L), as well as undetectable serum anti-Müllerian hormone (AMH) levels. Ultrasound revealed an atrophic and inactive left ovary, while small, irradiated uterus measured $34 + 20$ (cervix) mm $\times$ 24 mm $\times$ 24 mm. Endometrium was atrophic (1.2 to 2.3mm).

Because of the potential risk of disease retransmission via the ovarian graft despite harvesting during complete remission, the tissue was scrutinised for MRD in 2/11 cryopreserved fragments (Fig. 1). The initial size of each fragment was ~ $10 \times 5$ mm. In order to perform pregraft MRD screening, from each of these 2 initial fragments, a piece of $1 \times 5$ mm was used to perform PCR analysis and another piece of $4 \times 5$ mm was fixed for histology and immunohistochemistry. The remaining tissue, 2 fragments of $5 \times 5$ mm, was xenografted and distributed in the same manner as described above once retrieved. This was performed in collaboration with the Gynecology Research Laboratory at the Université Catholique de Louvain, Brussels, yielding the following results.

- Upon histological analysis (Supplementary Fig. 1), the patient's ovarian cortex exhibited a normal structure with follicle density exceeding 100 per 15 $mm^3$.
- Immunohistochemistry staining for myeloperoxidase (MPO), p53, CD4 and CD45 revealed no evidence of malignant cell contamination (Supplementary Fig. 2).
- Nested RT-PCR targeting the disease-specific MLL::AF9 fusion transcript in ovarian tissue was negative. The exact break-point of the fusion transcript was not known in our patient and a bone marrow sample at diagnosis was not available for additional analysis with current techniques. The analysed region included KMT2A (from exon 7 onwards, c.3750), extending to exon 11 of MLLT3. The presence of the transcript in the ovarian tissue was investigated by nested RT-PCR. Sensitivity of 0.001% has been reported for the MLL::AF9 fusion transcript [11].

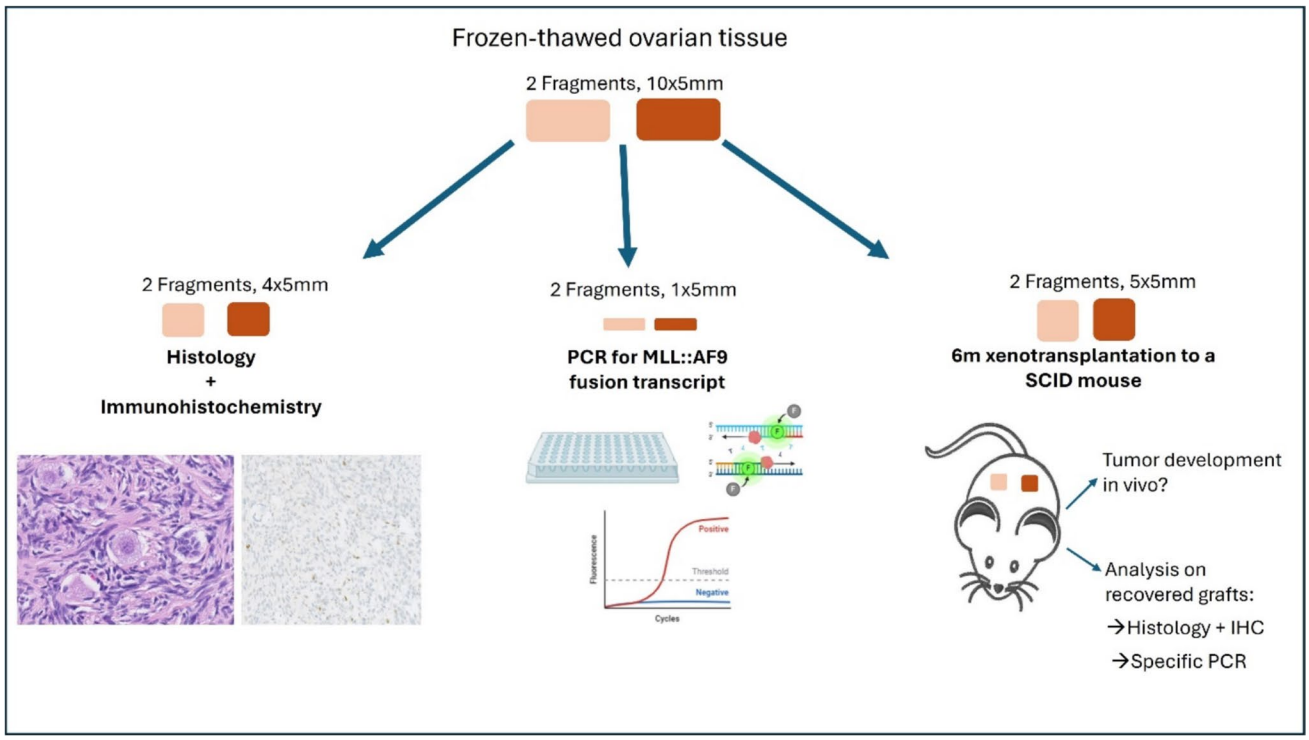


**Fig. 1** Minimal residual disease screening of ovarian tissue prior to transplantation. *The illustration for PCR was generated using biorender

– Our xenografting experiment involved 2 ovarian tissue fragments transplanted into a specially created peritoneal pocket of an immunodeficient SCID mouse for 6 months. Throughout the follow-up period, the mouse remained healthy, showing no signs of disease or suspicious masses. The mouse was sacrificed after 6 months. Intra-abdominal organs were examined for any macroscopic tumor development and, fortunately, none was identified. The grafted tissue was excised and analysed using the same parameters as described above, namely histology, immunohistochemistry and nested RT-PCR for the disease-specific MLL::AF9 fusion transcript. We also collected biopsies from the liver, spleen, bone and lungs. These were however not further analysed as the ovarian tissue was free from neoplastic invasion.

Given these reassuring results indicating a low likelihood of leukaemia cell contamination in the remaining cryopreserved tissue, it was agreed to proceed with transplantation after obtaining informed consent. In June 2021, 6 fragments of ovarian tissue were thawed and transplanted by laparoscopy (Fig. 2). The fragments measured 1 × 0.8 cm, 0.8 × 0.9 cm, 1 × 0.6 cm, 1 × 0.9 cm, 0.9 × 0.7 cm and 0.5 × 0.6 cm respectively. Due to the atrophic nature of the remaining ovary, the fragments were placed inside a constructed peritoneal window as previously described [2]. HRT had been initiated prior to transplantation and was discontinued three months post-transplantation, as it is known that endocrine function resumes around four months after grafting [3]. One month after stopping HRT, clinical and biological assessment revealed signs of graft activity and the presence of a corpus luteum upon ultrasound, accompanied by luteal phase serum hormone levels (progesterone 7.5 µg/L). Serum AMH was very low at 0.04 ng/mL.

On account of normal sperm values and permeability of the left fallopian tube, the patient underwent three cycles of follicle tracking with programmed intercourse 6 months after transplantation, which were unsuccessful. The patient then underwent 6 modified natural cycle (MNC)- Intracytoplasmic sperm injection (ICSI) procedures, as previously described by our team [12]. Briefly, after menstruation, ultrasound and hormone monitoring were conducted to track spontaneous follicle development. Once follicle diameter had reached 13 mm, 75 IU human menopausal gonadotropin (Menopur®) and 0.25 mg of ganirelix (Orgalutran®) were administered daily. Upon reaching 15 mm, recombinant human chorionic gonadotropin (Ovitrelle) was given, followed by transvaginal follicle aspiration 34–36 h later. After ICSI and embryo culture resulted in transfer of a cleavage-stage embryo on day 3 in 3 of the 6 cycles, with one biochemical pregnancy. Endometrial thickness always remained < 6.1 mm.

Between January and September of 2023, the patient underwent 6 more MNC ICSI attempts, but no embryo

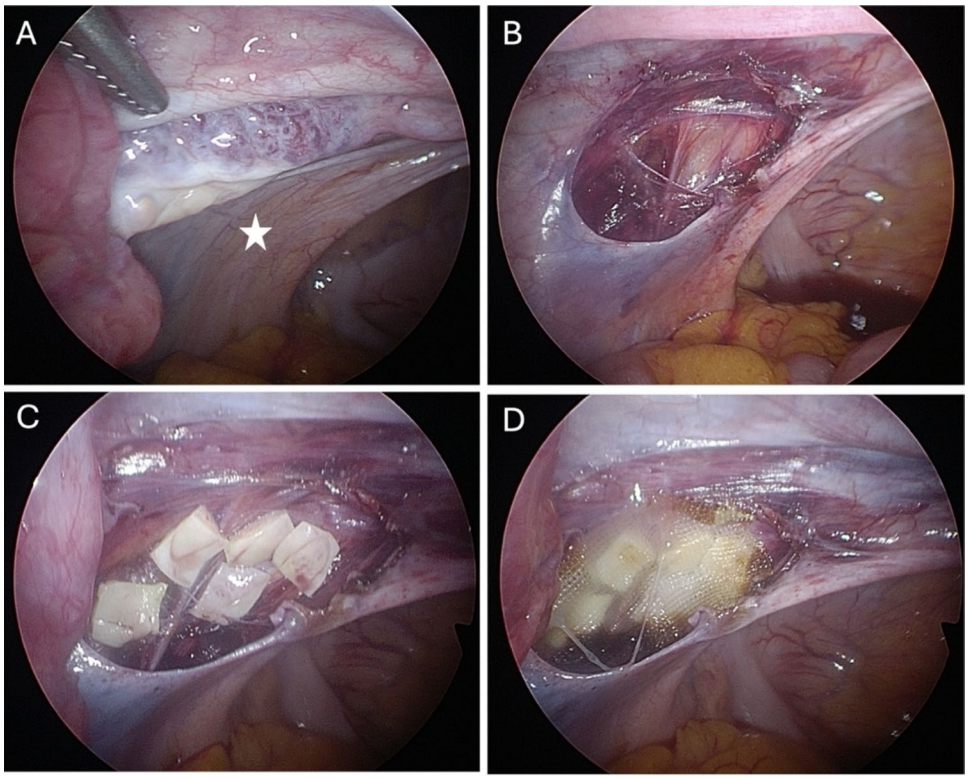


**Fig. 2** Ovarian tissue transplantation procedure: **A** shows the atrophic and inactive left ovary following gonadotoxic therapy. A peritoneal pocket was created (**B**) in the left ovarian fossa (* in **A**) and 5 fragments of frozen-thawed ovarian cortex were placed in the pocket with the medullar side in contact with the bed and the cortex facing upwards (**C**). Interceed, a bioabsorbable adhesion barrier, was placed over the fragments and secured with Tisseel glue to ensure proper fixation (**D**)

transfer. Challenges encountered included insufficient embryo quality (one cycle), failed fertilisation (two cycles) and no oocyte recovery (three cycles). Despite these discouraging outcomes, the patient was determined to pursue fertility treatment. In October 2023, a 13th MNC cycle was initiated. At the start of the cycle, the patient's FSH level was elevated at 15 IU/L. Ovulation was triggered on cycle day 8, with a follicle diameter of 15 mm, oestradiol level of 119 ng/L and endometrial thickness of 4.3 mm. Oocyte retrieval was performed 34 h later, yielding one mature oocyte, which was subsequently fertilised using ICSI. The resulting embryo displayed normal morphological development (see Supplementary video) and a 10-cell embryo was transferred on day 3 of development.

A successful pregnancy resulted from this embryo transfer and follow-up was uneventful until premature rupture of the membranes at 29 weeks. A caesarean section was performed due to signs of chorio-amnionitis, with delivery of a healthy boy at 34.5 weeks of gestation. Mother and child are doing well.

## Discussion

Acute leukaemia treated by myeloablative therapy is a common indication for OTC. However, due to the potential for malignant cell contamination in ovarian tissue retrieved from these patients [4–7], practitioners remain cautious about OTT. To date, only a few teams across the world have reported a limited number of cases of OTT in leukaemia patients after MRD screening [13–17]. To the best of our knowledge, this is the first reported livebirth in an AML survivor in Europe following OTT. In a published series of patients in Israel, four AML patients with negative MRD screening underwent OTT (8 OTT procedures) resulting in 4 LBs [18]. One AML survivor from the OTT series of Poirot et al. [13] has also conceived (C. Poirot, personal communication). No disease recurrence has been recorded among the transplanted cases to date.

Nevertheless, disease transmission has been observed after ovarian tissue xenografting from acute leukaemia patients to SCID mice [5, 18]. However, increasing evidence shows that the timing of tissue harvesting may impact the risk of disease transmission. Some studies show a clear correlation between bone marrow status at OTC and ovarian contamination [19], and tissue harvested during complete remission showed no leukaemia development in mice from different studies [20, 21]. It is therefore currently recommended that tissue be harvested during complete remission to decrease the risk of ovarian leukemic infiltration. However, caution is still warranteed, as some patients could present with preferential persistence of leukemic cells in ovary despite undetectable disease in bone marrow [22].

Molecular analysis targeting leukaemia-specific genetic markers offers better sensitivity than histology and immunohistochemistry for detecting cancer cells. Unfortunately,

AML often lacks disease-specific molecular markers. In our case, the presence of a fusion transcript specific to the disease allowed investigation of the ovarian tissue using highly sensitive methods, but a negative PCR on ovarian tissue does not guarantee the absence of MRD in remaining frozen tissue. Combining multiple detection methods, including xenografting of tissue samples, enhances levels of safety. Cases of disease transmission have been observed in mice following xenotransplantation, while other MRD detection methods were negative [5, 18]. Yet xenografting for MRD screening prior to OTT in leukaemia survivors has only been reported by one other group [18].

Cryopreservation of sufficient ovarian tissue for MRD assessment and bone marrow sampling upon diagnosis are crucial for up-to-date screening of molecular markers.

Another key consideration is that, in addition to POF, female leukaemia survivors treated with total body or abdominopelvic irradiation are also at risk of damage to the uterus [19, 20]. Mechanisms include direct radiation-induced changes, hypotrophy secondary to hypo-oestrogenism caused by ovarian injury, and direct damage caused by chemotherapy. The pathogenesis of late radiation sequelae is complex with individual variations in radiation sensitivity, but the uterus is more vulnerable prior to puberty [23, 24]. While an uneventful pregnancy is possible, these patients are exposed to a greater risk of adverse obstetric outcomes, including preterm birth and low birth weight, foetal growth restriction, uterine rupture, stillbirth and pre-eclampsia [23]. These risks need to be discussed and evaluated during the informed decision process and pregnancies must be closely monitored.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s10815-025-03447-z.

**Author contribution** M.S., M.D.B., I.D.Q., E.V.M., D.S., S.H. and M.D.V. were involved in the clinical procedures and A.C., C.H., I.M., I.S. and M.-M.D. were responsible for the laboratory procedures. M.S. and M.D.V. drafted the manuscript. All other authors critically reviewed the manuscript and approved the final version.

**Data availability** All data are available from the corresponding author [M.S.] on request.

**Code availability** Not applicable.

## Declarations

**Ethics approval** Not applicable.

**Consent to participate** The patients signed informed consent regarding publication of the data.

**Consent for publication** The patients signed informed consent regarding publication of the data.

**Competing interests** All authors declare that they have no conflict of interest with respect to the research, authorship, and/or publication of this article. M.D.V. has received speaker honoraria from Ferring and Gedeon Richter, outside the submitted work.

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