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Live Birth from Cryopreserved Oocyte After Uterus Transplantation: A Case Report

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Patient: Female, 28-year-old
Final Diagnosis: Mayer-Rokitansky-Küster-Hauser syndrome
Symptoms: Amenorrhea
Clinical Procedure: Uterus transplant
Specialty: Obstetrics and Gynecology • Transplantology

Objective: Rare disease

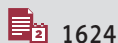
Background: Important legal and ethical issues must be addressed in the practice of uterus transplantation, because it is a non-life-saving intervention. In all cases reported in the literature so far, uterus transplantation is preceded by oocyte retrieval, fertilization of the collected oocytes, and subsequent freezing of the embryos produced. This element should be considered because of the potential ethical, legal, and moral implications related to the existence and fate of supernumerary embryos in the event of transplantation failure.

Case Report: The Italian Research Project for Uterus Transplantation from a brain-dead donor was approved in 2018 (No. 1438/CNT2018). A 28-year-old patient with Mayer-Rokitansky-Küster-Hauser syndrome, ectopic ovaries, and good ovarian reserve received uterus transplantation in 2020 after oocyte retrieval with laparoscopic assistance. Metaphase oocytes were cryopreserved and thawed after the successful transplantation to perform in vitro fertilization followed by embryo transfer. The pregnancy course was regular, without symptoms until week 30, when PCR positivity for SARS-CoV-2 was recorded. The patient underwent an emergency cesarean delivery at 34 weeks' gestation because of fever and the appearance of regular uterine contractions. An infant was born alive and vital at 34 weeks of pregnancy and weighed 1725 g. The newborn was discharged in good condition and with a body weight of 2740 g.

Conclusions: This case report shows that cryopreservation of oocytes can overcome the ethical issue related to embryo retrieval before a successful uterus transplantation can be demonstrated. Our result supports the possibility of bypassing embryo freezing before ascertaining the success of uterus transplantation.

Keywords: Embryo Transfer • Fertilization in Vitro • Oocytes • Transplantation

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Background

Uterus transplantation is performed to address infertility due to absolute uterine factors, including hysterectomy or Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome [1]. Since the first report in Sweden in 2014 [2], live birth after uterus transplantation from a living or deceased donor has been achieved in over 10 countries. A literature review published in 2021 showed a cumulative live birth rate in successful transplantation procedures above 80% in 62 published cases [3].

Uterus transplantation has some peculiarities. Success is determined only by the birth of a healthy child. Since the purpose of uterus transplantation is solely to get one or more pregnancies, it is followed by surgical removal of the graft to stop immunosuppression and related adverse events. Given the non-life-saving nature of uterus transplantation, safety for both the donor and the recipient, as well as ethical, legal, and financial issues, are very important.

Ovarian stimulation is performed before transplantation in order to retrieve and cryopreserve oocytes to ensure ovarian function prior to prolonged invasive surgery and immunosuppressive therapy, potentially decreasing the gonadal response [4]. An internationally recognized target is the retrieval of at least 6 good-quality blastocysts [5,6], and pregnancy is achieved by cryopreserved embryo transfer. Important ethical issues must be addressed regarding cryopreserved embryos in case of transplantation failure. For this reason, retrieval of at least 10 oocytes was identified as a requirement for inclusion on the waiting list for uterus transplantation at Cannizzaro Hospital (Catania, Italy). The laparoscopically assisted transvaginal oocyte retrieval in a patient affected with MRKH syndrome, with extra-pelvic ovaries but good ovarian reserve, has been previously reported [7].

Here, we report the first successful live birth case from a cryopreserved oocyte transfer after uterus transplantation.

Case Report

In 2020, a 28-year-old patient underwent uterus transplantation (**Figure 1**) at Cannizzaro Hospital (Catania, Italy) within the Research Project for Uterus Transplantation from a brain-dead donor (No. 1438/CNT2018), as previously published [6,8]. The project was approved by the Ethics Committee Catania 1 (protocol No. 0026684 on July 3, 2017). Briefly, the recipient had MRKH syndrome and blood group A+. In consideration of ectopic ovaries, laparoscopic-assisted oocyte retrieval was performed in 2018; 8 eligible oocytes were denuded 2 h after retrieval, and 6 metaphase II oocytes were selected for immediate vitrification.

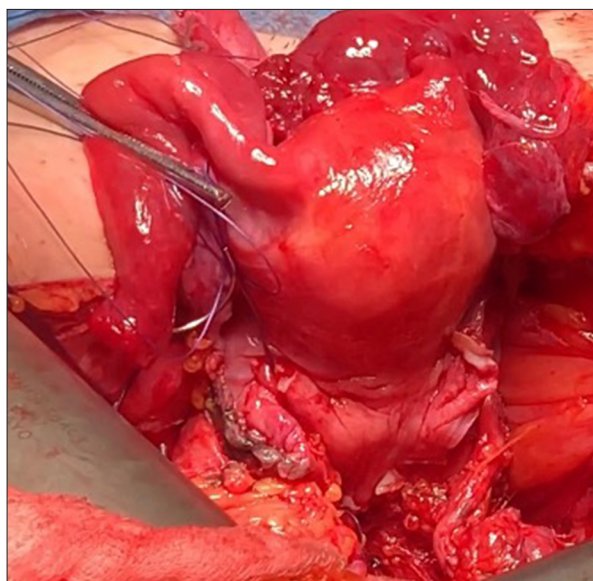


Figure 1. Transplanted uterus showing regular vascularization of the graft.

In August 2020, a uterus from a deceased donor became available at Careggi Hospital in Florence (Italy), compatible with the patient (2 cross matches). The recipient was informed that surgical removal of the received uterus might be subsequently recommended due to medical (ie, immunosuppression, rejection) or surgical (ie, cesarean delivery) complications.

After surgery, the patient underwent rejection monitoring and uterine trophism, evaluation by cervical biopsies, pelvic ultrasound with Doppler of the uterine vessels, and hormone dosages every 15 days for the first 3 months and then once a month for the next 3 months. All biopsies yielded grade 0 mucosal rejection, confirming the success of the uterus transplantation.

Seven months later, all the cryopreserved oocytes were thawed and inseminated, with a 100% fertilization rate (6 fertilized oocytes out of the 6 available). After the warming procedure, the oocytes were transferred into 1 mL of culture media (Sequential Cleav medium, Origio, Denmark) and cultured at 37°C (5.5% CO₂ and 5% O₂) in a K System incubator (G210 K system, Denmark) for exactly 2 h before intracytoplasmic sperm injection (ICSI). Fertilization was assessed at 16 to 18 h after ICSI. Fertilized oocytes were considered morphologically normal when 2 equally sized centrally located pronuclei were visible. Cleaving embryos were evaluated on day 2 after ICSI (44-46 h after insemination; **Figure 2**) with the use of a cumulative embryo classification scheme, taking into account the cleavage speed, blastomere symmetry, extent of fragmentation, and presence or absence of multinucleated blastomeres [9]. Around noon on day 2, cleavage embryos were transferred from Sequential Cleav medium to Blastocyst media (Sequential Blast, Origio, Denmark), while those not transferred

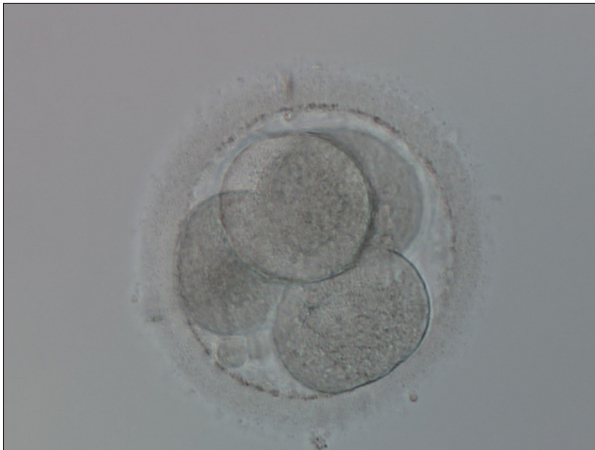


Figure 2. Cleaving embryo on day 2 after intracytoplasmic sperm injection: 4-cell embryo with four evenly sized blastomeres each one containing one nucleus (400× magnification).

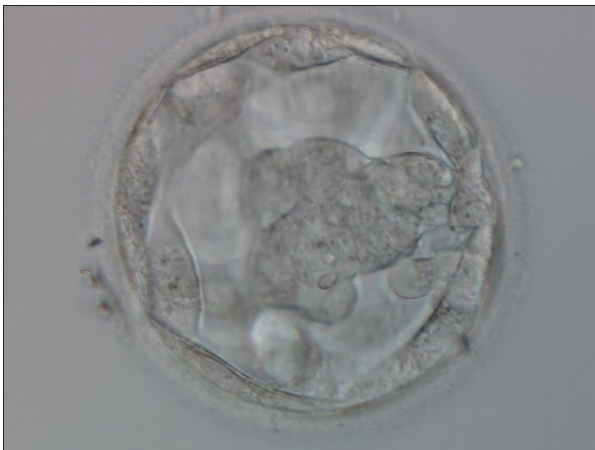


Figure 3. Blastocysts: Expanded blastocyst showing a large inner cell mass, which is made up of many cells that are tightly compacted (400× magnification).

were cryopreserved at the blastocyst stage (4 on day 5 and 1 on day 6) by vitrification (Fertipro Beernem, Belgium). The criteria for blastocyst formation were evaluated using the system of Gardner and Schoolcraft [9].

In January 2022, we successfully transferred a single vitrified and thawed blastocyst (Figure 3), achieving a viable pregnancy (Figure 4).

The pregnancy course was regular, without symptoms and pathologies until week 30, when PCR positivity for SARS-CoV-2 was recorded. The patient was hospitalized as a precaution, although she reported no symptoms related to COVID-19 disease. Corticosteroid prophylaxis was performed at the beginning of hospitalization and after 30 days. Finally, the patient underwent an emergency cesarean delivery at 34 weeks



Figure 4. Fetal profile ultrasound at week 30: Third trimester ultrasound revealed regular fetal development.

of gestation because of fever and the appearance of regular uterine contractions. Inflammation indexes were abnormal (white blood cell count 24, C-reactive protein 20 mg/dL, procalcitonin 46 ng/mL), but blood, urine, and vaginal cultures were negative. The patient was transferred after surgery to the Intensive Care Unit for therapy and monitoring, but the subsequent course was regular; therefore, she was discharged after 2 weeks in good health.

The female infant was born alive and vital and weighed 1725 g. The newborn was discharged in good condition and with a body weight of 2740 g.

Discussion

To the best of our knowledge, in all published live birth cases after uterus transplantation, assisted reproductive procedures have included blastocyst retrieval and vitrification before surgery, followed by embryo transfer performed within a variable time frame after surgery [2,10-15].

Our experience shows that the vitrification of oocytes followed by in vitro fertilization (IVF) after uterus transplantation can yield a viable pregnancy. This procedure was successful in a recipient with MRKH, extra-pelvic ovaries, and a good ovarian reserve. As a consequence of ectopic ovaries, oocyte retrieval was performed with laparoscopic assistance, which seems to overcome anatomical limitations, such as a short vagina and ectopic ovaries, expanding the options for patient eligibility [7,16].

Oocyte cryopreservation is a novel method in assisted reproductive technologies that aims at overcoming technical difficulties. The potential of a cryopreserved oocyte to lead to a live birth was calculated as 5% to 4.3%, although confirmation from larger samples seems necessary [17].

The procedure we used for assisted reproduction overcomes an ethical and legal issue, avoiding the cryopreservation of embryos before transplantation. The oocytes were cryopreserved until the surgical success of uterus transplantation was demonstrated, resulting in the option of embryo transfer. Only at this stage, embryos were produced by IVF. Notably, cryopreserved embryo donation is not currently permitted in Italy, which would deny the possibility of embryo transfer and implantation in case of uterus transplantation failure.

Currently, IVF is performed before uterus transplantation. This involves creating embryos before determining the success of the transplantation or the recipient's ability to carry a pregnancy to term. The issue of supernumerary human embryos produced in vitro, especially if transplantation is unsuccessful and embryos are left over from the assisted reproductive technology procedure, raises ethical concerns. The creation and disposition of human embryos, particularly supernumerary cryopreserved embryos, involves several interdisciplinary issues, including biotechnology, medicine, philosophy, morality, law, and bioethics [18]. Although the concept of the human embryo remains a topic of debate [19], the advancement of genetic research and experimentation techniques and the rapid progress in the biomedical field for treating severe human diseases make the issue of great interest. This discussion falls within the broader context of the legal protection and dignity of the human embryo, especially considering the growing importance of stem cell research in the clinical and biomedical fields.

The issue of embryos produced in excess due to assisted reproductive technology raises specific and additional problems for those produced in vitro and immediately transferred or for those conceived naturally. Unlike these categories, supernumerary embryos, despite having potential for future biological development, do not have the possibility of being born, as they are cryopreserved unless subsequently transferred indefinitely and stored in special banks until their natural extinction. Furthermore, in the context of IVF preceding uterine transplant, embryos are inherently created in excess, and although they are potentially usable for reproductive purposes, they are created regardless of the success of the transplantation or the recipient's ability to carry a pregnancy to term. This raises ethical, legal, and moral implications for the existence and fate of supernumerary embryos.

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Ostensibly, this case report addresses only one of the several ethical issues of uterus transplantation followed by assisted reproduction. The transplantation itself involves considering whether infertility should be a disease or not [20], should be publicly funded [21], and whether risks of complications for the donor and the recipient in a not-life-saving procedure are acceptable [22]. Additionally, ethical issues related to oocyte freezing, such as decisions about disposition, are still to be mentioned [23], together with the impossibility of transferring all the embryos obtained by IVF into the uterus.

Conclusions

A uterus transplantation from a deceased donor was successfully followed by live birth from a cryopreserved oocyte. This case report supports the possibility of bypassing embryo freezing before ascertaining the success of uterus transplantation.

In conclusion, we would like to take the opportunity of this case report to discuss whether it might be appropriate to create embryos only after ascertaining successful uterine transplantation: on the one hand, this approach does not seem to diminish the chances of pregnancy after transplantation; on the other hand, it prevents potential bioethical concerns due to embryos being created and cryopreserved in the event of uterine transplant failure.

Acknowledgements

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Ethics Statement

The present study was notified to the Ethics Committee of Policlinico of Catania (No. 1438/CNT2018).

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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