Case Report

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# First Twin Live-Birth Deliver After Oocyte Cryopreservation in a Follicular Lymphoma Patient

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**ABSTRACT**

Chemo- and radiotherapy can determine a severe gonadotoxicity compromising the reproductive potential of lymphoma patients and small numbers of successful pregnancies and live births from oocyte cryopreservation have been reported in cancer survivors. We describe the case of the first twin live birth obtained through fertilization of frozen-thawed oocytes in a woman with follicular lymphoma after first line treatment. Patient received 6 cycles of immunochemotherapy and 2 years of maintenance with rituximab obtaining a complete response. Two out of 12 thawed oocytes survived were inseminated, resulting in normal fertilization with development of two embryos. At week 36 of gestation, preterm prelabor rupture of membranes occurred. An urgent caesarean section was performed, resulting in the birth of two healthy males. Oncofertility counseling in young women in need of antineoplastic therapy is of great importance in order to minimize the impact of gonadotoxic treatment on their future lives.

**Abbreviations:** CHOP: Cyclophosphamide, Doxorubicin, Vincristine, Prednisone; FL: Follicular Lymphoma

## Introduction

Many young patients diagnosed with lymphoma achieve durable remissions with current treatment strategies and become long-term survivors. However, chemo- and radiotherapy can determine a severe gonadotoxicity and compromise their reproductive potential [1]. Therefore, the demand for fertility preservation has greatly increased during the last decades and the matter is particularly challenging when female patients are concerned [2,3]. Oocyte freezing and thawing proved to be an efficient method for fertility preservation [4,5]. Nevertheless, small numbers of successful pregnancies and live births from oocyte cryopreservation have been reported in female cancer survivors, especially in patients with hematological malignancies [6-8]. This is the first report of a follicular lymphoma (FL) patient who carried out a healthy twin pregnancy through fertilization of the oocytes cryopreserved before chemotherapy.

## Case Report

A 28-year-old nulliparous woman was diagnosed with non-Hodgkin FL, grade II, stage IIIA, in August 2014. She presented in

good clinical conditions, asymptomatic, and objective examination only showed superficial lymphadenopathies, the largest ones measuring about 5 cm in her groin. Before starting hematologic chemo-immunotherapy, the young woman was referred to the fertility preservation specialists at our Institution and, after appropriate counselling regarding the available options, she decided to undergo oocyte cryopreservation. Since the patient's hematologic condition did not contraindicate a moderate delay in the beginning of chemotherapy, controlled ovarian stimulation was performed: gonadotropins (follitropin α) associated with gonadotropin-releasing hormone agonist, namely leuprolide acetate. After 15 days of gonadotropin stimulation (the patient received a total dose of 1.575 IU), her estrogen level was 1.442 pg/ml and a transvaginal ultrasound showed 17 follicles ≥ 16 mm. Ovulation was triggered with α-chorionic gonadotropin (250 mcg). Fifteen oocytes were retrieved, 12 were cryopreserved through vitrification. No complications as ovarian hyperstimulation syndrome, bleeding or infection occurred after oocyte retrieval.

Ten days later, the patient started her hematologic treatment. She received 6 cycles of CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone) associated with 8 administrations of rituximab, obtaining a complete response which was confirmed after 2 years of maintenance with rituximab.

In May 2015, after the end of chemotherapy, the patient's menstrual cycle reappeared. She had fruitlessly tried to conceive for approximately 17 months when, in September 2018, she addressed the Infertility and In Vitro Fertilization Unit of our Hospital to research pregnancy with frozen oocytes. Endometrial preparation was performed with emiidrate estradiol patches, 300 mcg/day for 11 days. When the endometrial thickness reached 10 mm, 600 mg/day of micronized progesterone were added. Four oocytes were thawed; two of them survived and were inseminated through intracytoplasmic sperm injection, resulting in normal fertilization with development of two embryos which were transferred into the uterus on day 2 after insemination. After 14 days the serum level of β-human chorionic gonadotropin was 537 IU/l. Two weeks later, transvaginal ultrasound examination revealed two intrauterine sacs with embryo heart activity. Gestational diabetes mellitus, treated with diet and exercise, was the only medical complication of pregnancy.

At week 36 of gestation, preterm prelabor rupture of membranes occurred. An urgent caesarean section was performed, which resulted in the birth of two healthy males weighing 2690 g and 2610 g, respectively. Uterine atony/postpartum hemorrhage occurred after caesarean section and was treated with Bakri balloon tamponade inserted within the uterine cavity. Patient gave written informed consent to publish her data.

## Discussion

The increasingly prolonged survival of young lymphoma patients urges clinicians to focus on minimizing the long-term impact of antineoplastic treatment. An important issue is the potential toxicity of chemo- and radiotherapy on the gonadal function, which can lead young female patients to premature ovarian insufficiency and infertility [1]. Embryo cryopreservation is the most established option among assisted reproductive technologies, resulting in a pregnancy rate of approximately 30% [2]. More recently, oocyte cryopreservation has become a valid alternative for women who do not have a male partner and do not wish to resort to a sperm donor [3-5]. Overall, a small number of live births have been reported from fertilization of thawed oocytes in patients having received cancer therapies, most of them as single case reports or retrospective studies [6-8]. Some authors report that cancer patients tend to have a low ovarian reserve and an inadequate response to stimulation protocols, resulting in inferior numbers of oocytes retrieved when compared to age-matched non-oncologic women [9]. Others indicate that even the type of malignancy can influence the outcome of the procedure, with lymphoma patients showing lower levels of anti-mullerian hormone and needing higher doses of exogenous follicle-stimulating hormone compared to patients with solid tumors [10]. This aspect seems to be related to the high amounts of circulating inflammatory cytokines associated with this type of disease [10].

This topic is actually a matter of debate, since many other studies do not account for any significant difference in ovarian function among these categories of patients [11]. Another difference is that oocytes frozen for oncological reasons tend to face longer storage periods, due to the patient's need for prolonged treatment; nevertheless, it was demonstrated that time of storage does not affect cryopreserved oocytes in terms of gene expression, provided the freezing is done correctly [12]. In fact, data show that no higher incidence of genetic aberrations or birth defects is associated with the procedure.

## Conclusion

The case we described is, to our knowledge, the first twin live birth obtained through fertilization of frozen-thawed oocytes in a woman with a non-Hodgkin FL after first line treatment for the hematological malignancy. With this report, we aim to further stress the importance of oncofertility counseling in young women in need of antineoplastic therapy, in order to minimize the impact of gonadotoxic treatment on their future lives.

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