Successful fertility preservation by oocyte vitrification in a cancer patient: a case report

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Summary

Introduction: an essential part of comprehensive care for increasing number of young female survivors of malignant diseases is the preservation of fertility. Recent improvement in cryopreservation of metaphase II oocytes may offer a solution with minimum invasiveness and without the risk of transfer of malignant cells.

Materials and Methods: after the third recurrence of a bilateral borderline serous papillary ovarian carcinoma, a 23-year-old female patient was enrolled for fertility preservation before bilateral surgical cystectomy. After a mini flare-up stimulation protocol and hCG triggering 6 metaphase II oocytes were recovered and vitrified. Three years later secondary premature ovarian failure was diagnosed. After four years of storage the oocytes were warmed for in vitro fertilisation.

Results: four oocytes survived cryopreservation, and 2 of them fertilised after intracytoplasmic sperm injection. One embryo developed to 8-cell stage and was transferred to the uterus, resulting in a healthy boy weighing 4,110 g at week 41. A paediatric follow up of three years was performed.

Conclusions: this study reports the birth after oocyte vitrification in a patient with malignant disease. The increasing number of success proves the feasibility of oocyte vitrification to preserve fertility before cancer therapy with risk of subsequent ovarian failure and/or chromosome damage.

KEY WORDS: oocyte, fertility preservation, vitrification.

Introduction

Although the first baby after oocyte cryopreservation was born already in 1986 (1), attempts to increase efficiency have remained isolated and unsuccessful for long. It was the introduction of a highly efficient vitrification technique that resulted in the breakthrough, practically eliminating the differences between results with fresh vs cryopreserved oocytes (2). A kind of mitigated chain reaction has occurred, at the edge of legal boundaries in some countries, or just as the result of restrictive laws in the others, to use oocyte cryopreservation for two main purposes: oocyte donation, with relatively short turnover and high financial potential; and to replace the forbidden embryo cryopreservation, respectively (3, 4). Eventually, new application areas were also discovered including fertility preservation for medical indications, predominantly to avoid the potentially harmful effect of therapy in
young patients with malignant diseases (5, 6). The fact that major societies including European Society of Human Reproduction and Embryology (ESHRE), American Society for Reproductive Medicine (ASRM) and American Society of Clinical Oncologists (ASCO) acknowledged recently oocyte cryopreservation as a non-experimental procedure (7, 8) has provided the required legal and moral support for widespread application.

According to the nature of the intervention, outcomes of oocyte cryopreservation attempts performed to maintain fertility of young cancer patients are revealed after years, sometimes decades, and the most needed direct evidence, birth of healthy babies for feasibility of these approaches is sparse, so far. In this paper, we report a successful pregnancy and delivery with vitrified-warmed oocytes stored over 4 years.

Case description

In September 2006, a 20-year-old patient was referred to the gynecologist because of suspicion of adnexal disease. Sonographic evaluation revealed the presence of a large multilocular cyst with vascularized intracystic papillary projections (103x70x60 mm) on the right ovary and of a smaller multilocular vascularized cyst on the left ovary (27x22x30 mm). The patient underwent laparotomic bilateral cistectomy, omentectomy, appendectomy, multiple peritoneal biopsies and ascites aspiration. An intraoperative histological examination resulted in the diagnosis of papillary serous carcinoma of borderline malignancy. According to final histological and cytological analysis of specimens, the disease received stage IB according to FIGO guidelines. In February 2007 the patient was diagnosed with a bilateral recurrence of the ovarian cysts: multilocular cyst with vascularized intracystic papillary projections on the left ovary (27x22x30 mm). The patient underwent laparotomic bilateral cistectomy, omentectomy, appendectomy, multiple peritoneal biopsies and ascites aspiration. An intraoperative histological examination resulted in the diagnosis of papillary serous carcinoma of borderline malignancy. According to final histological and cytological analysis of specimens, the disease received stage IB according to FIGO guidelines. In February 2007 the patient was diagnosed with a bilateral recurrence of the ovarian cysts: multilocular cyst with vascularized intracystic papillary projections on the left ovary (27x22x30 mm) and on the right ovary (41x35x40 mm) and on the right ovary (48x37x45 mm). In March 2007 the patient underwent a second laparotomy for bilateral cystectomy. The final histological examination confirmed a recurrence of a borderline papillary serous ovarian tumour was confirmed. The oncologist conducted a strict follow-up and no recurrence of the disease was detected in the following 22 months. In 2012 the patient underwent two cycles of controlled ovarian stimulation for IVF but unfortunately both cycles were cancelled because of no ovarian response. Secondary premature ovarian failure was diagnosed (FSH 68 IU/L, LH 42 IU/L and E2 10 pg/ml).

In 2013, the patient was enrolled for artificial endometrial preparation for the oocyte warming cycle. One month later oocyte retrieval, the patient underwent laparotomic bilateral cystectomy. Recurrence of a borderline papillary serous ovarian tumour was confirmed. The oncologist conducted a strict follow-up and no recurrence of the disease was detected in the following 22 months. In 2012 the patient underwent two cycles of controlled ovarian stimulation for IVF but unfortunately both cycles were cancelled because of no ovarian response. Secondary premature ovarian failure was diagnosed (FSH 68 IU/L, LH 42 IU/L and E2 10 pg/ml).

In 2013, the patient was enrolled for artificial endometrial preparation for the oocyte warming cycle. After warming, 4 of 6 oocytes survived. Intracytoplasmic sperm injection was performed on 4 oocytes and 2 were fertilized. One embryo developed into 8-cell embryo and was trans-
ferred at Day 3. Intrauterine pregnancy was obtained as assessed by transvaginal ultrasonography at a gestational age of 6 weeks. The pregnancy resulted in the live birth of a healthy boy, weighing 4,110 g at week 41. Histology analysis of placenta confirmed absence of any potential metastatic disease. The newborn received the routinely perinatal care. The following pediatric check confirmed healthy status of newborns until the last check performed at 36 months post-delivery.

Discussion

In the United States, the estimated number of newly detected malignant diseases was close 800,000 in women in 2013 (11). Before reaching the age of 40, 1 out of 47-51 females will have to face this diagnosis, and approximately 1/3 of these patients will develop premature ovarian failure after the therapy (12, 13). The situation is similar in most countries in the world, including Italy. On the other hand, as the consequence of earlier diagnoses and more efficient therapies, the relative survival rate is slowly but continuously increasing. Accordingly more efforts are concentrated on the quality of life including maintenance of fertility (14).

As emphasized by the recent update of the American Society of Clinical Oncology (ASCO) Clinical Practice Guideline (7), options for fertility preservation depend on many factors including age, type of malignancy and treatment, family situation and likelihood that the malignant process is present in the ovary tissue. The decision of the patient is a crucial factor determining not only the fertility treatment but in some situations the therapy of the malignant process (15).

Apart from traditional ways including selection of conservative surgical interventions, ovary transposition before radiation, or application of ovary suppression with questionable outcome, currently available options are related to removal and extracorporal storage of reproductive cells and tissues (7).

Cryopreservation of ovaries seems to be the most feasible option, and currently the only available approach for pre-pubertal females. It can be performed without delay and does not require ovary stimulation. Both slow-rate freezing and vitrification seem to be appropriate, and the number of reported births is increasing (16-18). On the other hand, the removed ovarian tissue may contain malignant cells. Although re-occurrence was not reported so far, leukemia cells have already been identified in the cryopreserved ovary, contraindicating transplantation in such cases (19, 20). Ovary tissue cryopreservation also requires a double surgical procedure with inconveniences and potential complications, and in some cases, an additional in vitro fertilization treatment. In spite of the increasing number of births, the procedure is still regarded as experimental (7).

Cryopreservation of in vitro fertilized embryos and – very recently – in vivo matured oocytes are the two procedures definitely suggested by the ASRM and ASCO (7, 8) for fertility preservation of women diagnosed with malignant diseases at the fertile age. Earlier concerns regarding the time-consuming and potentially harmful hormonal stimulation seem to diminish as randomly started stimulation performed with selected agents may minimize the dangers (12, 21, 22).

As embryo vitrification is a routine procedure in almost all IVF laboratories, with widely acknowledged success rates and millions of babies born, it is usually regarded as the first option (12). However, it has to be considered that fertility preservation may mean postponement of the pregnancy and birth with decades, up to 40 years or, considering the ongoing tendencies, possibly even more. The legal, family or ethical situation of the patient may change radically during this period. Oocyte cryopreservation may offer much more flexibility to overcome the problems related to the new situation. Another important fact is that, according to a recent report, more than 90% of women with malignant diseases choose oocyte vitrification over alternative fertility preservation methods (23). This approach allows in fact preserving the reproductive the women autonomy (24).

In long term, in vitro maturation of oocytes and cryopreservation either before or after maturation may also become an option, however, at present the overall efficiency of the approach seems to be low (25, 26).

In a review, Cobo et al. (27) listed 5 published live births from 5 different clinics between 2007 and 2013 after therapy of malignant diseases where fertility was preserved through oocyte cryopreservation. In the first 2 cases, oocytes were cryopreserved by slow-rate freezing, in 1
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case both slow-rate freezing and vitrification were used resulting in twins, and in the last 2 reports vitrification was the method of choice. More recently Martinez et al. (28) reported 5 live births after oocyte vitrification before anticancer treatments. Good assisted reproductive technology performance and good perinatal outcomes were reported.

Different studies have reported similar outcomes using autologous vitrified oocytes or fresh oocytes (29-31). These findings are especially reassuring for fertility preservation application and the age-associated estimates of oocyte to live-born child efficiencies calculated particularly useful for patient counselling.

To our knowledge, the present case is the first successful delivery by a cancer patient with vitrified-warmed oocytes in Italy. The slowly increasing number of births worldwide may encourage practitioners to select oocyte vitrification for fertility preservation of young females with malignant diseases.

References


