ORIGINAL ARTICLE: FERTILITY PRESERVATION

Oocyte vitrification versus ovarian cortex transplantation in fertility preservation for adult women undergoing gonadotoxic treatments: a prospective cohort study

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Objective: To compare the efficacy of oocyte vitrification (OV) with that of ovarian cortex cryopreservation and transplantation (OCT) in women undergoing gonadotoxic treatments.
Design: Prospective observational cohort study.
Setting: Not applicable.
Patient(s): Candidates for chemo-/radiotherapy who joined our fertility preservation (FP) program were included in this study between 2005 and 2015. One cohort included 1,024 patients undergoing OV; the other cohort included 800 patients undergoing OCT.
Intervention(s): OV using the cryotop device and OCT using a slow freezing protocol.
Main Outcome Measure(s): Live-birth rate (LBR) and clinical pregnancy rate (CPR).
Result(s): Basal antimüllerian hormone levels of the patients revealed no differences in ovarian reserve before FP (OV, 11.6 pM [5.4–24.7]; OCT, 11.8 pM [6.4–21.9]). In the OV cohort, 49 patients used the vitrified oocytes after a mean storage time of 3.9 years. In the OCT cohort, 44 sought pregnancy after a mean storage time of 5.5 years. A trend toward higher CPR and LBR (per patient) was observed in the OV group (risk ratio [RR_{CPR}], 1.31 [95% confidence interval, 0.90–1.92]; RR_{LBR} 1.39 [95% confidence interval, 0.95–2.03]), although differences were not statistically significant. In the OCT group, 46.7% of pregnancies occurred spontaneously and no pregnancy was achieved when the tissue was harvested beyond the age of 36 years. All patients except three undergoing OCT resumed or improved endocrine ovarian function.
Conclusion(s): Although we observed a trend toward higher LBR after OV, OCT is a very effective method to preserve fertility, allows for natural pregnancy, and restores ovarian function. In clinical scenarios where OV is not feasible, OCT remains the FP technique of choice and should no longer be considered experimental. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Oocyte vitrification, ovarian cortex cryopreservation and transplantation, fertility preservation

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Fertility preservation (FP) procedures are increasingly requested because of higher cancer survival rates associated with oncological treatments, making FP an integral component of the holistic management of oncologic patients (1–4). However, close to 30% of women undergoing gonadotoxic treatments are not properly informed of FP options (5). Counseling should be individualized based on the risk of gonadal failure, depending upon multiple factors including the prognosis of the patient, her age and ovarian reserve, the level of gonadotoxicity linked to specific drugs and regimens, and the amount of time available before the start of chemotherapy, radiotherapy, or surgery (2).

Currently, embryo and oocyte vitrification (OV) are the established FP methods (1–4). Embryo vitrification requires a male counterpart and permanently links further fertility to that same partner. OV, however, postpones the contribution of a male counterpart and is a reproducible, safe, and effective technique (6, 7). Live-birth rates (LBRs) as a result of OV depend on the number of available mature oocytes vitrified; this number will, in turn, depend on the number of ovarian stimulation cycles done before the gonadotoxic treatment is administered, as well as the age of the patient at the time of vitrification, which may affect survival rates after warming, embryo development, and LBRs (7).

Ovarian cortex cryopreservation and transplantation (OCT) is considered an experimental technique (1, 3), mainly due to a lack of evidence regarding its efficiency and the risk of reintroduction of malignant cells. Despite an increasing number of successful reports of OCT procedures (8–13), with more than 75 live births reported so far, there is a paucity of data concerning retransplantations. OCT is often considered as the first option for FP when there is not enough time to complete ovarian stimulation for OV or in prepubertal patients (2). Orthotopic OCT can restore ovarian function and allow natural fertility, with unlimited oocyte retrievals, as long as the graft is active.

We sought to compare the results of OCT with that of OV in two large cohorts of patients to establish the efficacy of the latter as compared with that of the former. In 2005, we implemented an FP program for oncology patients. Due to national regulations, OCT could only be offered in tertiary hospitals, while OV could be performed in both hospitals and fertility clinics. For this reason, all patients undergoing OCT were centralized in one institution (La Fe University Hospital), while the patients undergoing OV were referred to any of the institutions participating in our network (La Fe University Hospital-IVF Unit or IVI clinics). To date, the number of FP procedures performed in our centers accounts for more than 57% of the OV procedures and more than 72% of the OCT done for medical reasons in Spain, according to the registry of the Spanish Fertility Society (www.registrosef.com).

MATERIAL AND METHODS

Study Design and Study Population

Female patients with medical conditions requiring gonadotoxic treatments were sent to one of the program's institutions (La Fe University Hospital, n = 1,150; or IVI clinics, n = 895) between January 1, 2005 and December 31, 2015. Our FP program grants access to FP techniques without any economic cost to the patients and covers the same population nationwide. All referred patients were counseled according to the same management algorithm (Supplemental Fig. 1). Patients undergoing pelvic radiotherapy, whole-body irradiation, or chemotherapy including alkylating agents were in general proposed to undergo FP, although the risk of infertility was adjusted on individual parameters described as predictors of ovarian failure in the literature: age, ovarian reserve markers (antral follicle count and antimüllerian hormone [AMH]), and treatment protocol. Patients postponing maternity for medical reasons beyond the age of 38 were also included (for example, patients needing long-term hormonotherapy after breast cancer, even if they did not receive any type of chemotherapy). Patients were included in the study if they had 5–10 year survival rates over 50% and if they underwent OCT or OV. Patients older than 40 years, undergoing both OCT and OV, undergoing embryo vitrification, or not undergoing any of the techniques were not included in the study. Patients requiring OCT were redirected to La Fe University Hospital, and patients requiring OV were treated either in La Fe University Hospital or in IVI clinics. Two observational cohorts were defined: the OV cohort included patients undergoing ovarian stimulation for OV, and the OCT cohort included patients undergoing ovarian cortex retrieval and cryopreservation. Patients wishing to conceive and considered to be disease free with no formal contraindication for pregnancy were offered the use of their cryopreserved oocytes or tissue if they presented with amenorrhea, had a premature ovarian insufficiency (POI) defined according to the European Society of Human Reproduction and Embryology criteria (14), were over 40 years of age, or had undergone assisted reproductive technology treatments without success.

Variables regarding the demographic characteristics of the patients, the diseases motivating the FP, and the parameters of ovarian stimulation and ovarian cortex retrieval were prospectively collected using the SIVIS and DONAGEST databases. The ovarian reserve of the patients before FP was quantified using AMH determinations (Beckman Coulter AMH Gen II ELISA and automated chemiluminescence AMH assay on Roche Modular E170 analyzer from 2014).

Ethical Approval

This study was approved by the Institutional Review Board of La Fe University Hospital (2011/0018) and IVI group (1505-VLC-033-AC), and informed consent was obtained from the patients.

Oocyte Vitrification

Our protocols for controlled ovarian stimulation (COS), OV and warming, endometrial preparation, and luteal phase support have been described in detail elsewhere (15) and are available as Supplemental Material.

Ovarian Cortex Transplantation

Ovarian tissue was retrieved laparoscopically unless contraindications existed for general anesthesia. In such cases, the tissue was obtained by minilaparotomy under spinal anesthesia.