ORIGINAL ARTICLE: FERTILITY PRESERVATION

Oocytes vitrification as an efficient option for elective fertility preservation

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Objective: To provide a detailed description of the current oocyte vitrification status as a means of elective fertility preservation (EFP).
Design: Retrospective observational multicenter study.
Setting: Private university-affiliated center.
Patient(s): A total of 1,468 women who underwent EFP because of age or having associated a medical condition other than cancer (January 2007 to April 2015).
Intervention(s): None.
Main Outcome Measure(s): Survival and cumulative live birth rate (CLBR) per consumed oocyte.
Result(s): Mean age was higher with EFP due to age versus having an associated medical reason (37.7 y [95% confidence interval (CI) 36.5–37.9] vs. 35.7 y [95% CI 34.9–36.3]). In total, 137 patients (9.3%) returned to use their oocytes. Overall survival rate was 85.2% (95% CI 83.2–87.2). Live birth rate per patient was higher in women ≤35 years old than ≥36 years old (50% [95% CI 32.7–67.3] vs. 22.9% [95% CI 14.9–30.9]). CLBR was higher and increased faster in younger women. The gain in CLBR was sharp from 5 (15.4%, 95% CI −4.2 to 35.0) to 8 oocytes (40.8%, 95% CI 13.2–68.4), with an 8.4% gain per additional oocyte, in the ≤35-year-old group. The increase was slower with 10–15 oocytes, reaching a plateau CLBR of 85.2%. A milder increase (4.9% gain) was observed in the ≥36-year-old group (from 5.1% [95% CI −0.6 to 10.7] to 19.9% [95% CI 8.7–31.1] when 5–8 oocytes were consumed), reaching the plateau with 11 oocytes (CLBR 35.6%). Forty babies were born.
Conclusion(s): At least 8–10 metaphase II oocytes are necessary to achieve reasonable success. Numbers should be individualized in women >36 years old. We suggest encouraging women who are motivated exclusively by a desire to postpone childbearing because of age, to come at younger ages to increase success possibilities. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: Fertility preservation, oocyte vitrification, survival rate, live birth

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Egg banking via vitrification has proved an efficient technique in assisted reproduction (1–3). Currently, there are consolidated vitrification programs in assisted reproductive technology (ART) clinical practice, which has led to an increasing number of children born with the use of this technique. At present, almost 6,000 (5,842 up to December 2014) live births after the vitrification of oocytes have been accounted for in our group (unpublished data). The health of infants and the obstetrical evolution of the pregnancies conceived with vitrified oocytes are similar to those observed in our population of children conceived with fresh oocytes, thus endorsing the safety of the technique (4). Growing evidence for the efficacy and safety of female gamete vitrification has led both the American Society for Reproductive Medicine and the European Society for Human Reproduction and Embryology to not consider this technique to be experimental (5, 6).

For these reasons, vitrification of oocytes is currently being offered as an option for women who wish to preserve their gametes to allow them to have a chance to conceive in the future and to have their own genetic offspring (7). The main beneficiaries of this

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strategy are cancer patients who must undergo chemotherapy or radiotherapy and patients with other diseases who require potentially gonadotoxic treatments. Ovarian tissue cryopreservation has been applied to cancer patients for fertility preservation (FP) purposes. Another population to benefit from FP is made up of those women who wish to postpone childbearing for various reasons usually known as "social reasons." The biggest threat in these cases is age, which is why this indication is also known as elective FP (EFP) due to age-related fertility decline (5). EFP can also help women to endure some medical conditions other than cancer that can trouble their future fertility, such as endometriosis or other alterations that lead to premature menopause. In these cases, the condition itself is not an impediment to getting pregnant at the time of diagnosis, but, for a variety of reasons, they decide to postpone motherhood; therefore, they choose to vitrify their oocytes for future IVF treatments. In a significant proportion of cases, they are diagnosed when planning the vitrification cycle, or if previously diagnosed, they go on with the EFP after being counseled by their specialist. On the other hand, there are other medical conditions that contraindicate pregnancy at the time of diagnosis, such as some disorders that require potentially iatrogenic treatments, e.g., autoimmune diseases, or even a clinical situation that entails having to undergo bilateral ovariectomy. EFP is strongly advisable in these cases.

Currently, assisted reproduction centers are noticing a considerable increase in the demand for EFP requests for all the above reasons. All of the women seek a "time-out" until they reach the right time to try to get pregnant. In many cases they need to overcome particular situations, including lack of a partner, need to solve financial or career issues, and many others. Solving these particular situations usually implies that they need to take their time, which means that an undetermined time period will pass before they decide to come back to use their oocytes. Given these particuliarities, knowledge of the women's real possibilities is still lacking. Therefore, they have sought counseling about their possibilities based on assumptions that originate from outcomes achieved in other populations, namely, oocyte recipients and other infertile patients, after oocyte vitrification.

With the present study, we aimed to provide a detailed description of the current situation of EFP in our group, including the profile of the woman who vitrified oocytes, the description of the rate at which they return to use their oocytes, their clinical outcomes and the probability of having a baby according to the number of oocytes consumed. This study provides data on the outcomes attained after EFP via oocyte vitrification, achieved in actual FP patients to avoid extrapolations from other populations. This information will be most welcome, because evidence on this matter is lacking.

MATERIALS AND METHODS

Study Design and Study Population

A retrospective multicenter study included all of the women (n = 1,468) who electively vitrified their oocytes for FP purposes because of age or having an associated medical condition other than cancer from January 2007 to April 2015 at 13 different Spanish clinics from our group. Institutional Review Board approval was obtained (1505-VLC-033-AC). Data were collected from computerized clinical charts and were anonymized according to Spanish law on assisted reproduction (Law 14/2007 on Biomedical Research). The vast majority of the included women (n = 1,382) opted for EFP because of age-related fertility decline (social reasons). The reason the remaining women (n = 86) chose FP was the presence of a medical condition other than cancer that could undermine future fertility, such as endometriosis or low ovarian reserve. Overall, 137 women returned to use their oocytes. A small group of six patients (seven controlled ovarian stimulation [COS] cycles) with a disease that required a potentially iatrogenic treatment or on a therapy that discouraged gestation during the medical management time also vitrified oocytes for FP during the study period time. The diseases involved were transverse myelitis, thyroid nodule, and multiple sclerosis (the latter patient also needed bilateral ovariectomy owing to the presence of teratoma). None of these patients had returned to use their oocytes at the time of writing.

Controlled Ovarian Stimulation Protocol

COS was initiated on day 2 or 3 of a spontaneous cycle. An initial dose of 225–300 IU recombinant FSH (rFSH; Gonal-F [Merck-Serono] or Puregon [MSD]) and/or highly purified hMG (Menopur; Ferring Pharmaceuticals) was administered. From day 6 onward, the gonadotropin dose was estimated according to serum E_2 levels and a transvaginal ultrasound scan. When a leading follicle reached 13–14 mm, a GnRH antagonist (Cetrotide [Merck-Serono] or Orgalutran [MSD]) was administered at 0.25 μg/d. Final oocyte maturation was triggered with the use of 250 μg recombinant hCG (rhCG; Ovitrelle [Merck-Serono]) as soon as the mean diameters of two follicles were $\geq$18 mm. In some cases, triggering was performed with a single dose of a GnRH agonist (0.1 mg triptorelin [Decapeptyl; Ipsen Pharma]). Oocyte retrieval was scheduled 36 hours after hCG injection.

Oocyte Vitrification and Warming

Oocytes were denuded 2 hours after oocyte retrieval. Following the nuclear maturity evaluation, only the metaphase II (MII) oocytes were selected for immediate vitrification. All the vitrification and warming solutions were obtained from Kitazato. The Cryotop method used for oocyte vitrification has been described elsewhere (2). Briefly, after 12 minutes of stepwise equilibration in a mixture of 15% (v/v) ethylene glycol + dimethylsulfoxide, oocytes were subjected to a vitrification solution for 50–60 seconds that contained 30% (v/v) of the same cryoprotectants. Hydroxypropyl cellulose, as a substitute for synthetic serum substitute, and trehalose, as a substitute for sucrose, were also used in the solutions for vitrification and warming. No statistical differences were found in either survival or clinical outcomes when the differential use of these additives was tested (data not shown). The preliminary study results have been previously revealed (8). Loading took place within the