Chapter 10
Clinical Outcome After Oocyte Cryopreservation for Elective Fertility Preservation

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Fertility preservation (FP) is an emerging, rapidly evolving branch of reproductive medicine comprising the preservation of gametes (sperm, oocytes), and reproductive tissue (ovarian, testicular), giving individuals at risk of losing their reproductive ability the chance to conceive and have their own genetic offspring. Cancer patients to undergo surgery or start chemotherapy or radiotherapy, other medical conditions leading to premature menopause, and healthy women wishing to postpone childbearing, are the main beneficiaries of this strategy. Options for women to safeguard their fertility include the cryopreservation of ovarian tissue or oocytes.

The preservation of biological materials at cryogenic temperatures (cryopreservation) allows complete stopping of biological reactions with the aim of preserving the viability of the cells while keeping intact the tissue physiology after the transplantation of organs or in the case of gametes, to preserve unaltered their ability to produce embryos able to generate viable pregnancies and healthy babies. Efficient cryopreservation of oocytes has helped greatly as a tool for FP especially during the last 10 years. More specifically, the introduction of vitrification into assisted reproduction (AR) has established efficient female gamete cryopreservation, which provides comparable outcomes to those achieved with fresh oocytes [1, 2] and opens up a wide range of applications, including FP [3].

Elective Fertility Preservation (EFP) for Social Reasons

In today's society, many women who are taking long strides in their careers and delaying pregnancy further away from the younger years of childbearing. This trend affects mainly the developed countries most of which are experiencing a

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D. Stoop (ed.), *Preventing Age Related Fertility Loss*,
DOI 10.1007/978-3-319-14857-1_10

significantly reduced birth rate. Women are often forced to choose advancement of career, financial security, and certain social pressures ahead of their biological clock, the well-known decline in fertility over 30s. With more women deciding to delay motherhood, there is an increase interest in the availability of the current cryopreservation technologies in order to safeguard their options for the future.

A compilation of the first series of outcomes achieved when women who vitrified their oocytes due to EFP in our centres returned to attempt pregnancy was published in 2013, providing the first report on babies achieved after elective fertility preservation for social reasons [3]. Therefore, five babies were reported. Concomitantly, the birth of a baby boy whose mother had non-Hodgkin lymphoma when she vitrified her oocytes prior to the oncological treatment was also reported [3]. A more recent review of our data published in 2016 provide a detailed description of the situation of EFP in our group, including the profile of the woman who have vitrified, 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 [4]. The study included 1468 women, while most of them (N = 1382) opted for EFP due to age related fertility decline (social reasons). The reason why the remaining women chose EFP (N = 86 patients) was the presence of a medical condition, other than cancer, which could undermine future fertility, as endometriosis or low ovarian reserve. Of them all, 137 women returned to use their oocytes.

Among several interesting findings we observed in this population, it is worth highlighting the age at vitrification and how it impacted on final outcomes. In our experience, most women are deciding for EFP at advanced age. Accordingly, 63% of them came to vitrify at ages between 37 and 40, additionally, a not inconsiderable 16.2% were aged ≥40 years old by the time of vitrification, while conversely, the vast minority were younger than 30 years of age [4]. As expectable, the age at vitrification had great impact on different outcomes related to the number of oocytes retrieved and the number of MII finally vitrified, oocytes' survival, pregnancy and live birth rates. Larger number of oocytes were either retrieved or vitrified in patients aged 35 years or younger when compared to patients older than 35 years. Furthermore, the lowest figures were observed in patients aged 40 years or older (5.1 (95% CI = 4.2–6.0) mean retrieved and 3.9 (95% CI = 2.6–5.0) mean MII vitrified).

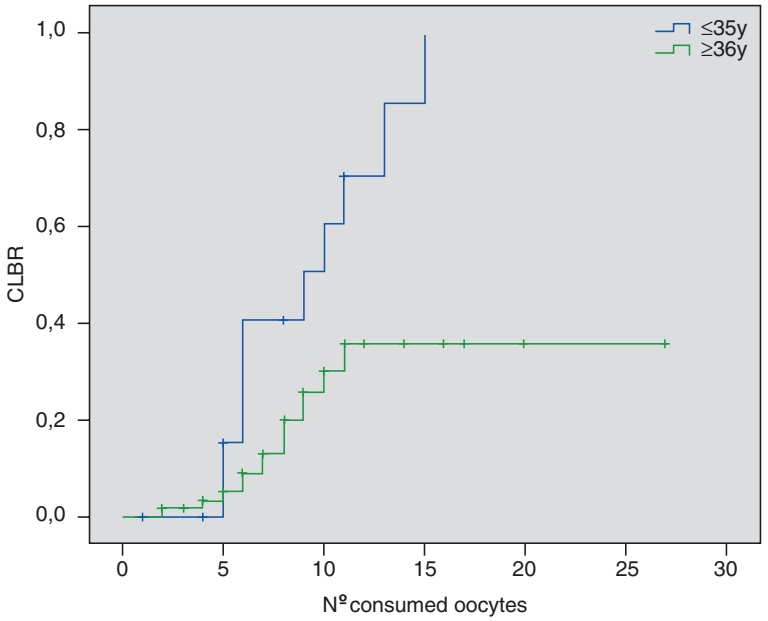
As shown in Table 10.1 [4], survival was higher in the group of women aged ≤35 years (94.6% [95% CI = 91.9–97.3] vs. 82.4% [95% CI = 79.9–84.9]). The live birth rate per patient was statistically higher in younger patients when compared to the older ones (50% [95% CI = 32.7–67.3] vs. 22.9% [95% CI = 14.9–30.9]). Table 10.1-Panel II. shows the outcomes according to different subgroups of age showing the noticeable decrease in the live birth rate from the youngest category including women aged ≤29 years (100% [95% CI = 100–100]) to the oldest group of women aged 40–44 years (3.7% [95% CI = −3.4–10.8]).

The cumulative probability of having a child according to the number oocytes consumed by the statistical approach using Kaplan Meier was also assessed (Fig. 10.1) [4]. If women were 35 years or younger, we observed a huge difference in the cumulative live birth rate (CLBR) when using only five oocytes (15.4%) com-

Table 10.1 Clinical outcome according to age at vitrification

Age	N° patients	N° cycles	Survival rate	CPR/cycle	CPR/ET	OPR/cycle	OPR/ET	N° Live birth /patient
I. Survival and clinical outcome in patients aged ≤35 years and ≥36 years at vitrification								
≤35	32	41	257/272 (94.6)[a]	24/41 (58.5)[a]	24/39 (61.5)[a]	21/41 (51.2)[a]	21/39 (53.9)[a]	16/32 (50)[a]
≥36	105	150	750/910 (82.4)[b]	47/150 (31.3)[b]	47/118 (39.8)[b]	27/150 (18.0)[b]	27/118 (22.9)[b]	24/105 (22.9)[b]
Total	137	191	1007/1182 (85.2)	71/191 (37.1)	71/157 (45.2)	48/191 (25.1)	48/157 (30.5)	40/137 (29.2)
II. Survival and clinical outcome according to different groups of age at vitrification								
≤29	6	9	59/62 (94.5)[a]	6/9 (66.6)[a]	6/9 (66.6)[a]	6/9 (66.6)[a]	6/9 (66.6)[a]	6/6 (100)[a]
30–34	20	23	155/161 (96.1)[a]	14/23 (60.9)[a]	14/21 (66.7)[a]	13/23 (56.5)[a]	13/21 (61.9)[a]	9/20 (45)[b]
35–39	84	127	601/734 (81.8)[b]	48/127 (37.8)[b]	48/112 (42.9)[b]	27/127 (21.3)[b]	27 /112 (24.1)[b]	24/84 (28.5)[b]
≥40	27	32	192/225 (85.3)[b]	3/32 (9.8)[c]	3/15 (20)[c]	2/32 (6.3)[c]	2/15 (13.3)[b]	1 (3.7)[c]
Total	137	191	1007/1182 (85.2)	71/191 (37.1)	71/157 (45.2)	48/191 (25.1)	48/157 (30.5)	40/137 (29.2)

CPR clinical pregnancy rate, *OPR* ongoing pregnancy rate, *ET* embryo transfer
Different superscripts in the same column indicate statistical differences ($P < 0.05$). Includes embryo cryo-transfers. Cobo et al. Fertil Steril 105 [3]: 755–764 e758 [4]



≤35 years old		≥36 years old	
N° oocytes	CLBR (IC95%)	N° oocytes	CLBR (95% CI)
5	15,4 (-4.2-35.0)	5	5,1 (-0.6-10.7)
8	40.8 (13.2-68.4)	8	19,9 (8.7-31.1)
9	50,6 (31.6-79.6)	9	25.8 (12.7-38.9)
10	60,5 (34.5-89.5)	10	29,7 (15.2-34.2)
15	85,2 (60.5-100)	11	35,6 (18.4-52.8)

Fig. 10.1 CLBR according to age (≤35 and ≥36y) and number of oocytes consumed. Cobo et al. Fertil Steril 105 [3]: 755–764 e758 [4]

pared to employing eight (40.8%) which means an 8.4% increase in CLBR per additional oocyte. On the other hand, if they were 36 years or older using the same number of oocytes the increase in CLBR was considerably milder (from 5.1% CLBR using 5 oocytes to 19.9% when 8 oocytes were consumed, meaning an increase in CLBR of 4.9%). Moreover, the success rate achieved in the younger group (≤35 years) was twice the achieved in the older group of women aged ≥36 years (60.5% vs. 29.7% respectively) when 10 oocytes were used. With 15 oocytes the CLBR continue to increase in the ≤35 years group, whereas with the same number of oocytes the plateau was already reached in the group of women aged ≥36 years, meaning that at this point the success is independent from the number of oocytes used up. In light of this, we suggest that at least 8–10MII should be vitrified

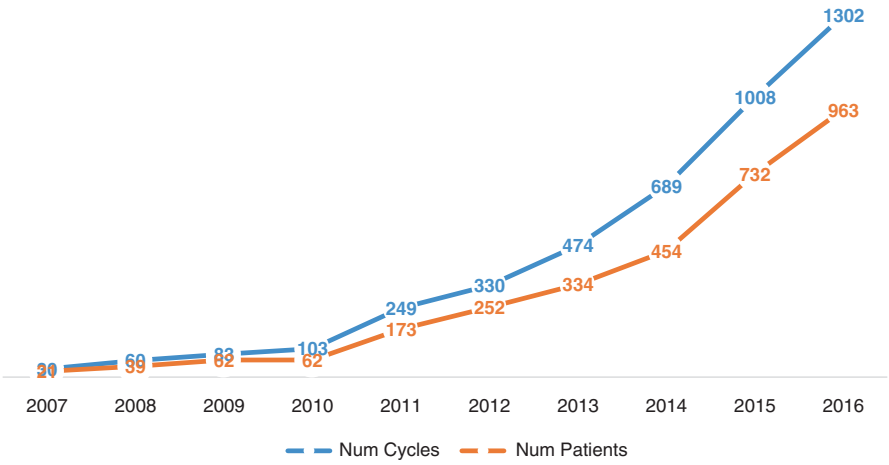


Fig. 10.2 Trends of the utilization of oocytes vitrification as a strategy for elective fertility preservation during the past 9 years. Number of patients and vitrification cycles are shown

to obtain a reasonable success rate. In women older than 36 years, numbers should be individualized along with the possibility of offering PGS.

All these findings have helped to consolidate the approach of oocytes vitrification in cases of elective fertility preservation, fact that has contributed to the increase in the number of women deciding for this strategy as a way to alleviate the pressure posed by their every particular circumstance. In accordance, the most recent analysis of our data on fertility preservation of for social reasons during the 9 years of this practice in our setting shows clear increasing trends in the application of oocytes vitrification for EFP (Fig. 10.2). A total of 3092 patients have conducted 4328 (1.4 ± 1.1) vitrification cycles for EFP from September 2007 to December 2016. Most of them had high educational level (74.8%), while the majority were heterosexual single women (77.9%). The remaining women were heterosexual married women (21.6%) and only 0.5% were homosexual.

Mean patients' age at vitrification was 37.2 ± 3.9 years old. As shown in Fig. 10.3, the great majority (73.6%) decided for oocytes vitrification between 35 and 40 years old, which is the age at which most women consult for AR treatments, due to the well-known age-related fertility decline. As shown in Fig. 10.4, among the 353 patients who have returned to use their oocytes nearly 80% vitrified at ages between 35 and 41 years. Additionally, shorter storage time was observed for patients older than 36 years old when compared to those aged 35 or lower (1.7 ± 0.6 vs. 2.9 ± 1.4 years of storage respectively). The debate is then served, since as we demonstrated earlier (Table 10.1) the efficiency in terms of live birth rate per patient is much lower in patients older than 36 years old and worsens dramatically at 40s [4]. In light of these findings, patients should be counsel to decide earlier for oocytes vitrification. However, another debate related to cost-effectiveness becomes relevant, being that recent data shows that egg banking for fertility preservation is more cost-effective in women under the age of 38 years [5, 6].

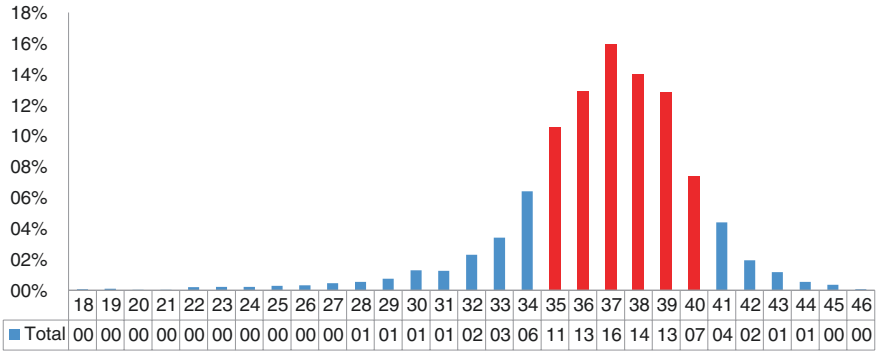


Fig. 10.3 Distribution of patients age at vitrification

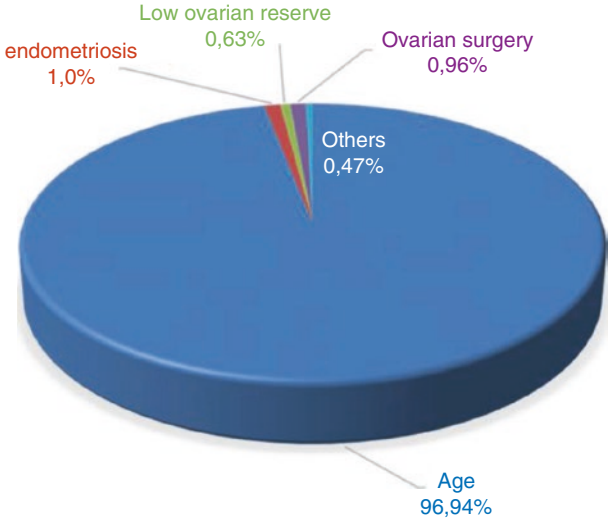


Fig. 10.4 Distribution of women who had returned to use their oocytes in the 9 years of EFP in our centers (2007–2016)

Although the two arguments are valid, we think that it is absolutely necessary to adequately inform the patients both the very young women, and enlightening them that the probability of using their cryo-stored eggs in the upcoming years is reduced, due to, in the future; their chance of natural conception could remain high. On the other hand, older women, who are more likely to use their cryo-savings, should be accurately informed about their reduced reproductive chances. Anyway, as we have demonstrated, a child can be achieved when oocytes were vitrified over 40s, making very difficult to set upper limits for applying the strategy.

Table 10.2 Clinical outcome after 9 years of applying elective fertility preservation (2007–2016)

Elective fertility preservation		
		IC95%
Patients returning	353	
Warming Cycles	373 (1.1 ± 0.05)	1.09–1.2
Mean warmed oocytes/patient	3245 (9.2 ± 4.8)	9.1–9.3
Survival rate	2641 (81.4)	81.1–82.7
Number of transfers	252 (71.4)	65.8–76.9
Mean embryos Transferred	384 (1.03 ± 0.8)	0.9–1.1
IR	36.7	31.4–43.4
CPR/transfer	116 (46.4)	40.3–52.6
OPR/transfer	85 (34.1)	28.3–40.0
N° Live Birth	63	
Cryotransfers of surplus embryos		
N° patients	81	
N° warming cycles	110 (1.4 ± 0.1)	1.3–1.4
N°ET	143 (1.8 ± 0.5)	1.7–1.9
N°Cryo transfers	106	
IR	35.7	27.9–43.6
CPR/transfer	49 (46.2)	36.7–55.7
OPR/transfer	32 (30.2)	21.5–38.9
N° Live Birth	21	
Total Live birth	84	
C Live birth rate/patient	23.8	19.4–28.2

Figure 10.4, shows the distribution of 3092 women who conducted EFP in our units during the period of 2007–2016. Table 10.2 shows a summary of clinical outcomes achieved when the 353 women returned to attempt pregnancy with their vitrified oocytes. A total of 3245 oocytes were warmed up (mean = 9.2 ± 4.8; 95% CI = 9.1–9.3). The overall survival rate was 81.4% (N = 2641 oocytes; 95% CI = 81.1–82.7). A number of 384 (mean per patient = 1.03 ± 0.8 95% CI = 0.9–1.1) embryos were transferred in 252 embryo transfers (mean per patient = 71.4; 95% CI = 65.8–76.9). Implantation rate was 36.7% (95% CI = 31.4–43.4) and clinical and ongoing pregnancy rates were 46.4% (95% CI = 40.3–52.6) and 34.1% (95% CI = 28.3–40.0) respectively. Sixty-three healthy babies were born.

A number of 81 patients who had surplus embryos for additional cryotransfers performed 110 embryo- warming cycles (mean/patient = 1.4 ± 0.1). A mean of 1.8 ± 0.5 embryos were transferred in 106 cryo-transfers (mean/patient = 1.3 ± 2.5) achieving 35.7% implantation rate. Cumulative Clinical and ongoing pregnancy rates considering fresh and all cryo-transfers were (53.6% and 40.8% respectively). Twenty-one babies were born from these cryo-transfers. The cumulative livebirth rate per patient was 23.8% (95% CI = 19.4–28.2), being higher in younger women (51.3% when patients vitrified at 35 years or earlier vs. 16.2% when they were older than 35 years at vitrification).

In conclusion, the efficiency of oocytes vitrification for save guarding fertility is currently a consolidated option that can be offered to women seeking an option to achieve motherhood in the future. However, we think it is mandatory to explain to women who seek EFP that oocyte cryo-storage is no insurance policy to secure future motherhood, but a means to increase the chances of having a biological child, and that these chances depend on age and on the number of oocytes stored. It is imperative that women are informed about the drop in the probability of success over the age of 35 years. The number of vitrified oocytes should be adjusted according to the patient's age in order to increase the probability of having a child, irrespectively of oocytes coming from one stimulation cycle or more. In cases of EFP, women should be encouraged to decide this option when younger than 35 years due to greater biological efficiency, although the strategy could be less cost-effective at younger ages.

Key Points

1. The clinical outcome with the use of vitrified oocytes is comparable to outcomes achieved with fresh oocytes
2. Currently, mostly women perform elective oocyte vitrification between the age of 35 and 40 years.
3. The efficiency in terms of live birth is much lower in patients performing oocyte vitrification after the age of 36 years and worsens dramatically after the age of 40.
4. Women who consider elective oocyte cryopreservation should be encouraged to do so before the age of 35, although this could be less cost-effective.
5. It remains important to counsel women that elective oocyte cryopreservation can increase future reproductive chances but cannot guarantee reproductive success.

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