Oocyte vitrification for fertility preservation for both medical and nonmedical reasons

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Growing evidence of successful outcomes achieved with the oocyte vitrification technique has greatly contributed to its application in the field of fertility preservation (FP). The population that can benefit from FP includes women at a risk of losing their ovarian function because of either iatrogenic causes or natural depletion of their ovarian reserve. Therefore, oncological patients and healthy women who wish to delay motherhood for various reasons—elective FP—are currently being offered this option. Satisfactory oocyte survival rates and clinical outcomes, including cumulative live birth rates, have been reported in recent years. These studies show that age at oocyte retrieval strongly affects reproductive prognosis after FP. Therefore, elective FP patients should be encouraged to decide before they reach the age of 35 years to significantly increase their chances of success. The effect of age has also been observed in patients with cancer and women diagnosed with endometriosis. The reproductive outcome after FP is worse in patients with cancer, but a direct association between the disease and reproductive outcome is yet to be proven. Young patients ($\leq$35 years) with endometriosis who have undergone cystectomy before oocyte retrieval for FP have worse outcomes than nonoperated women in age-matched groups. In addition, the number of oocytes used per patient is closely related to success in all populations, with considerable improvement in the result with the addition of a few oocytes, especially in healthy young patients. (Fertil Steril® 2021;115:1091–101. ©2021 by American Society for Reproductive Medicine.)

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The purpose of fertility preservation (FP) is to preserve both male and female gametes for individuals whose reproductive function is threatened by various reasons. Cryopreservation of the female gamete for FP occurred during the second half of the 2000s, concomitantly with the upsurge and escalation of efficient oocyte vitrification. Nevertheless, the history of oocyte cryopreservation is fraught with failures, beginning with the publication of the first success achieved via slow freezing in 1986 (1), followed by practically no reports of successful results in the subsequent years of continuous efforts. This negative trend began to change with the emergence of vitrification. Thus, the first baby born using this technology was reported in 1999 (2). Nonetheless, the existing protocols still had to be improved, and it was years later when publications with consistent results started to appear (3) as a consequence of the emergence of more refined vitrification protocols (4).

The successful use of vitrified oocytes in ovum donation (5, 6) has greatly contributed to the development of egg banking, which might soon go beyond donation programs to be applied in other indications. Available evidence of the safety of the technique, confirmed by the lack of increase in adverse obstetric and perinatal outcomes in in vitro fertilization (IVF) cycles using vitrified oocytes, has also contributed to the advancement of this approach (7–9). As a result, oocyte vitrification is currently being used in different clinical situations in assisted reproduction (AR). In this context, it has been applied to build larger cohorts of poor responders (6, 10) or help increase the number of euploid blastocysts in preimplantation genetic testing for aneuploidy cycles (11, 12). The vitrification of oocytes or embryos is also useful when delay in fresh embryo transfer has been recommended because of a high risk of hyperstimulation syndrome (13). Egg banking of autologous gametes is also useful when the number of oocytes to inseminate is limited by legal restrictions (14) or even personal choices. The strategy also helps to solve unexpected situations in which the partner's semen sample is not available.

Although oocyte vitrification has been useful in all these situations, which are likely to occur regularly in AR, the technique of preservation of

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the female gamete was initially conceived as a strategy to safeguard the reproductive potential of patients whose future fertility was threatened by medical conditions, such as cancer or other diseases (15). Ovarian damage, which leads to infertility, is a frequent adverse effect of chemotherapy; so, FP is increasingly being offered, before the initiation of oncological treatment, to women diagnosed with cancer. Although mature oocyte vitrification is currently the most widely applied strategy for FP in patients with cancer (16), this option is not useful in prepubertal patients, to whom ovarian cortex cryopreservation should be offered. The usefulness of FP is not limited only to patients with cancer but is also of great help in other pathologies in which the ovarian reserve is threatened, either by the disease itself or, iatrogenically, by the necessary treatment. In these cases, an intervention to safeguard gametes for future use is required to maintain the fertility potential. Hence, the other potential candidates for FP are women diagnosed with ovarian endometriosis (17). This disease is known to compromise the ovarian function, which is why it is strongly associated with infertility in different scenarios, including natural conception, intrauterine insemination, and assisted reproductive technology (18). Endometriosis leads to a chronic systemic inflammatory process and predisposition to anatomic, tubal, and ovulatory changes; it is present in up to 50% of infertile couples (19). This is why FP is being increasingly proposed to these patients to counteract endometriosis-related infertility, safeguarding their reproductive chances by vitrifying their oocytes for future use (20). Furthermore, patients diagnosed with ovarian endometrioma frequently need repetitive conservative surgery for the ovaries, which can also lead to premature ovarian failure by diminishing the ovarian reserve, which, in turn, results in pregnancy rates being reduced almost by half after a primary surgery (21). Therefore, patients with endometriosis are the perfect candidates for FP.

Another relevant branch of FP is known as elective fertility preservation (EFP) or FP to postpone parenthood. This alternative represents a great step forward in AR and has been one of the most relevant contributions to this field of medicine in recent years. Because of the potential role of EFP in modern society, it has even been compared to the effect, back in the days, of the appearance of a contraceptive pill. An increasing number of women in modern societies are delaying childbearing beyond their reproductive age. The lack of a partner is one of the most common reasons for choosing EFP (22). Additionally, EFP aids with women's emancipation by giving them the chance to focus on their career or other goals in life apart from motherhood, providing them with the opportunity to become pregnant in the future, whenever they wish, using their own gametes (23). The current evidence is helpful in clarifying the efficiency and, therefore, the true potential of this alternative (24).

This review focuses on the currently available evidence of the results of the use of mature oocyte vitrification as a strategy for FP in different populations, including patients with cancer, for medical reasons other than cancer, such as endometriosis, and in women who electively vitrified their oocytes for EFP, with special focus on the main factors related to success in all the different populations.

FP IN ONCOLOGICAL PATIENTS

Although there is evidence of successful outcomes after mature oocyte vitrification (3, 25), the current proportion of women diagnosed with cancer who are offered or at least informed of this option for FP remains small. Currently, the literature offers little evidence of the clinical outcomes of women who opt for oncological fertility preservation (onco-FP). This may be because the population that decides on this option is not very large yet even though oocyte vitrification as an option for safeguarding fertility in oncological patients has been available for slightly over 10 years. In fact, a large study published in 2018 showed that of all oocyte vitrification procedures within the Instituto Valenciano de Infertilidad network, 2% were performed in the context of onco-FP (26). Likewise, the population of women returning to use their oocytes was still very low. In the same publication, which, to the best of our knowledge, is the largest report published to date on the use of vitrified oocytes after onco-FP, the return rate in the oncological group was only 7.2% (26).

The first live birth documented was achieved in 2007 using the slow-freezing method (27). A woman with Hodgkin lymphoma was offered the option of freezing mature oocytes before chemotherapy. A year later, the birth of healthy twins was also reported with the use of the slow-freezing method in an ovariectomized patient with borderline cancer (28).

Once oocyte vitrification was established as a successful method, it was accepted as a viable option for FP by international societies (29, 30) and became the method of choice for the preservation of the female gamete (31). A summary of the oocyte survival rates and clinical outcomes in patients with cancer and other populations is shown in Table 1 (32–42). The first case, reported in Europe, of a pregnancy after FP using oocyte vitrification was achieved in a woman diagnosed with atypical medullar breast cancer who initially had cryopreserved ovarian cortex tissue before chemotherapy (32). Subsequent to the grafting of the cryopreserved tissue, 16 mature oocytes were vitrified after 4 stimulation cycles. The patient gave birth to healthy twins. The cryotop method, initially introduced in the early 2000s (4), was employed in this study and has become one of the most widely applied methods in routine practice. A year later, Kim et al. (33) reported the birth of the first baby born after oocyte vitrification in a patient with chronic myeloid leukemia after 9 years of storage. Nonetheless, they used electron microscope grids for vitrification, which are no longer used in clinical practice because of technical difficulties involved.

In 2013, another study reported clinical data on 4 women with cancer who had vitrified their oocytes for FP and returned to use them; the birth of a healthy boy was reported (34). In this series, a total of 340 (71.5%) of 475 women diagnosed with cancer opted for oocyte vitrification. An interesting aspect of this study was that it also provided results of ovarian response and parameters of controlled ovarian stimulation in patients with cancer. The mean (±SD) number of metaphase II (MII) oocytes retrieved per patient was 8.5 ± 6.4 even though patients with hormone-sensitive tumors were given a lower total dose of gonadotropins. A great majority of

TABLE 1

Oocyte survival rates and clinical outcomes with the use of vitrified oocytes for fertility preservation in different populations.

Author	Indication	No. of patients	No. of warming cycles	No. of warmed oocytes	Survival rate (%)	Clinical pregnancy rate (%)	Live birth rate (%)
Sanchez-Serrano et al., 2010 (32)*	Onco-FP	1	1	9	100	100	100
Kim et al., 2011 (33)	Onco-FP	1	1	7	71.4	100	100
García-Velasco et al., 2013 (34)*	Onco-FP	1	1	4		25	25
	EFP	26	26	191	84.8	42.3	19.2
Alvarez et al., 2014 (35)	Onco-FP	1	1	8	87.5	100	100
Da Motta et al., 2014 (36)	Onco-FP	1	2	19		50	50
Martinez et al., 2014 (37)	Onco-FP	11	11	65	92.3	54.5	
Perrin et al., 2016 (38)	Onco-FP	1	1	5	100	100	100
Cobo et al., 2016 (24)*	EFP	137	148	1,182	85.2	46.2	20.9
Doyle et al. 2016 (39)	EFP		128	1,283	86.1	57.1	38.6
Specchia et al., 2019 (40)	Onco-FP	11	14	73	86.3	30.8	15.4
Diaz-Garcia et al., 2018 (16)*	Onco-FP	49			77.3	36.4	29.1
Cobo et al., 2018 (26)*	EFP	641	680	5,830	83.9	50.7	33.7
	Onco-FP	80	81	605	81.8	41.4	31
Wennberg et al., 2019 (41)	EFP	38	49	393	78		26.3
Cobo et al., 2020 (42)*	Endo-FP	485	529	4,531	83.2	45.9	46.4

Note: Totals have not been calculated because the studies marked with asterisks (*) belong to the same investigators; therefore, the data may be overlapping. EFP = elective fertility preservation; endo-FP = fertility preservation in patients with endometriosis; onco-FP = oncological fertility preservation.

Cobo. FP results—elective and medical reasons. Fertil Steril 2021.

the oncological patients included in this study were diagnosed with breast cancer (67%), which is why the use of letrozole, an aromatase inhibitor, was indicated for ovarian stimulation in patients with hormone-sensitive tumors (43). Consequently, the mean estradiol levels were lower in the onco-FP group. Another study published in 2018 showed that both the number of retrieved and MII-vitrified oocytes were lower when the group of patients with cancer receiving letrozole was compared with patients affected by other types of cancer who were stimulated using an antagonist protocol (26). Nonetheless, the same study showed that the overall ovarian response was not impaired in patients with cancer when compared with patients in the nononcological EFP group (number of MII-vitrified oocytes per patient = 9.5 ± 2.6 vs. 9.8 ± 6.4, respectively; not significant). Indeed, when calculated per cycle, the number of oocytes was higher in the onco-FP group (8.7 ± 6.9 vs. 7.3 ± 5.6; $P<.05$), most probably because the patients with cancer were significantly younger than the women in the EFP group. The evidence of ovarian response in patients with cancer is still contradictory: there are studies that showed an unaltered ovarian response (44–47), whereas others reported a compromised ovarian reserve when patients with cancer were compared with age-matched controls (48). Some investigators have suggested a relationship between the type of cancer and ovarian response to controlled ovarian stimulation (COS), showing lower oocyte retrieval level in patients with breast cancer (49), whereas other studies have suggested a compromise in the ovarian response because of *BRCA* mutations (50, 51).

Another publication reported that a 28-year-old woman diagnosed with invasive mucinous ovarian carcinoma, whose vitrified oocytes were stored before fertility-sparing surgery with uterus preservation, gave birth to a healthy boy (35). That same year, other investigators reported successful delivery in a patient who had overcome breast cancer and had 28 MII oocytes vitrified for FP (36). In this study, the patient returned 6 years later seeking IVF treatment with these oocytes.

A subsequent report (37) included an update of a publication by Garcia-Velasco et al. (34) in 2013. In this publication, 11 patients returned to be treated with their vitrified oocytes (return rate = 3.1%) after a period ranging from 6 months in a woman with endometrial carcinoma to 5 years in women with breast cancer (mean storage time = 2.5 years). All the women underwent embryo transfer (mean no. of embryos transferred = 1.8 ± 0.7), and fetal heartbeat was confirmed in 4 of them (clinical pregnancy rate = 36.4%). The 4 women delivered at 39.5 ± 0.5 weeks of gestation. Favorable obstetric outcomes and no birth defects were observed in the 4 babies born (mean weight = 3,115 ± 346.5 g). This confirmed previous observations regarding the absence of adverse obstetric and perinatal outcomes after oocyte vitrification compared with cycles using fresh oocytes (7, 8). In 2016, Perrin et al. (38) reported the first live birth in France after FP in an oncological patient who had her oocytes vitrified before the treatment of a grade-IV Hodgkin lymphoma.

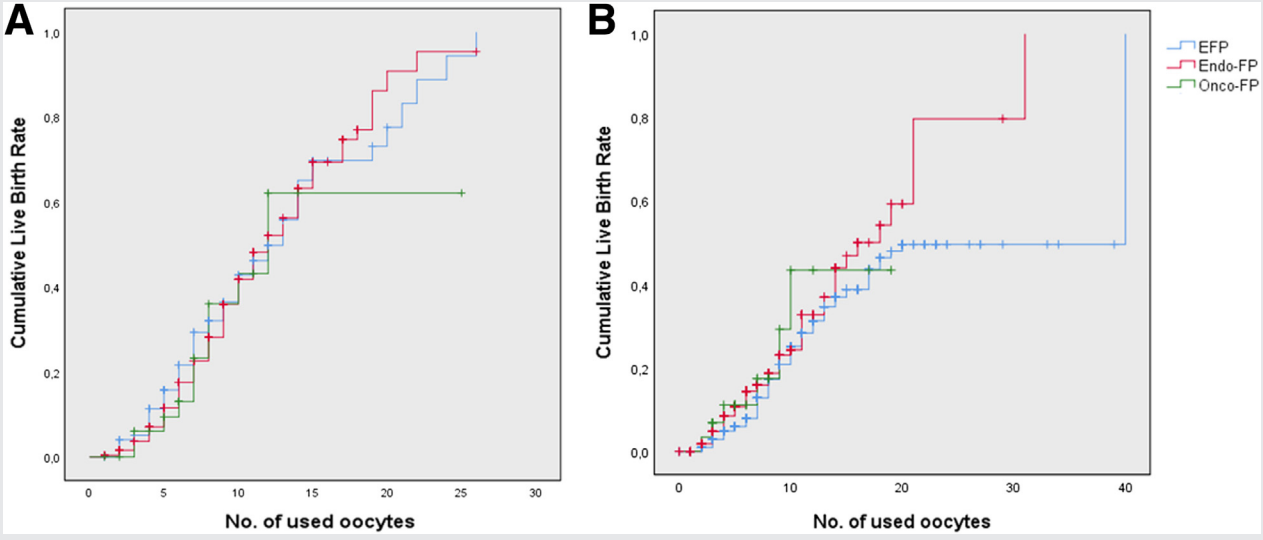
Based on the report of the first baby conceived using vitrified oocytes for FP from 2007 (27) to 2018 (26), most of the studies reporting clinical data on the use of vitrified oocytes in onco-FP, including live birth rates, have been case reports.

The study published by Cobo et al. (26), the largest to date, included 1,073 women (1,172 vitrification cycles) diagnosed with cancer and 5,289 women (7,044 vitrification cycles) who chose EFP because of age-related fertility decline. This report assessed ovarian stimulation and IVF parameters in all the members of both the populations who opted for FP as well as clinical outcomes for women of both the groups who returned to attempt pregnancy. The study also analyzed factors related to success rates. Most patients (64.6%) in the onco-FP group were diagnosed with breast cancer, followed by women with Hodgkin (11.6%) and non-Hodgkin lymphoma (5.2%). The mean age at the time of oocyte retrieval was 32.3 ± 3.5 years, and the mean number of oocytes retrieved per patient was 8.7 ± 6.9. After a mean storage time of 4.1 ± 0.9 years, 80 women came back to use their stored oocytes. The oocyte survival rate was 81.8%, and after transferring a mean number of 1.4 ± 0.1 embryos, the clinical and ongoing pregnancy rates were 41.4% and 31%, respectively. A total of 25 healthy babies were born, including second transfers of surplus embryos stored after fresh transfers.

A study published a year later reported the outcomes of 11 women who returned to attempt a pregnancy (return rate = 4.3%) (40). This study reflected 18 years of experience in a tertiary referral center; so, both the slow-freezing and vitrification methods were used for cryopreservation.

When analyzing the results of assisted reproductive technology, it is of utmost relevance to consider the age of the patient. The study considering both populations, onco-FP and EFP, showed that significantly older age in the latter was behind the lower oocyte yield observed in this group (26). However, despite this result, the implantation rate was significantly lower in the group of patients with cancer (32.6% vs. 42.5%). Furthermore, when comparisons were made with age-matched groups, the differences became even more significant: the oocyte survival rate (91.4% vs. 81.2%), clinical pregnancy rate (65.9% vs. 42.8%), and cumulative live birth rate (CLBR; 68.8% vs. 42.1%) were strongly impaired in the onco-FP and EFP groups with patients aged ≤35 years. This finding, and the assumption made by others that cancer is a systemic condition, allowed the hypothesis that an underlying disease in the onco-FP group can probably impair reproductive outcome. However, the effect of the sole presence of cancer on oocyte survival and CLBR was not statistically confirmed (26). Conversely, a strong effect of age was shown: the odds ratio for oocyte survival was 1.922 (95% confidence interval = 1.274–2.900; $P = .025$). In addition, the odds ratio adjusted to consider the COS parameters did not show a relationship between COS and oocyte survival or CLBR. Most likely, in this study, despite the poorer outcome in the onco-FP group, no association between the indication and result could be statistically proven because of the small sample size of the group of patients with cancer who returned to use their oocytes after FP. Further larger studies will be needed to elucidate this issue. On the other hand, if the patients included in the sample analyzed had been treated with radiotherapy, the possible impact on the endometrium might have affected implantation. The combined association of indication and age with oocyte survival and CLBR was also observed in a different publication (52). The effect of age on CLBR in 3 different populations is shown in Figure 1 and

FIGURE 1



Kaplan-Meier plot of cumulative probability of live birth for patients who underwent EFP (*blue*), endo-FP (*red*), and onco-FP (*green*) according to the number of oocytes used. Overall comparisons (log rank [Mantel-Cox], Breslow [generalized-Wilcoxon], and Tarone-Ware) showed no statistical differences in both age groups, with $P = .889$, .749, and .882, respectively, for women aged ≤35 years (**A**) and $P = .169$, .236, and .249, respectively, for older women (**B**). EFP = elective fertility preservation; endo-FP = fertility preservation in patients with endometriosis; onco-FP = oncological fertility preservation.

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Table 2. The results were similar in the patients of the onco-FP, EFP, and endometriosis (endo-FP) groups when they used the same number of oocytes in age-matched groups, thus revealing age as one of the most powerful factors impacting the final outcome (CLBR).

FP FOR MEDICAL REASONS OTHER THAN CANCER: PATIENTS WITH ENDOMETRIOSIS

Endometriosis poses severe threats to the ovarian reserve, making these patients suitable candidates for FP. Despite the obvious advantages of offering FP to women with this disease, the widespread use of FP is still the subject of some debates (20). The discussion revolves mainly around the limited information regarding the efficiency of FP in this particular population and lack of evidence of the quantity and quality of the oocytes retrieved. However, above all, most uncertainties are related to cost-effectiveness because systematically offering FP to patients with endometriosis might have a dramatic effect on public health (20). This issue was also recently highlighted as one of the weaknesses of the strengths, weaknesses, opportunities, and threats analysis approach (53). Hence, it is essential to select the best candidates among patients with endometriosis to offer them the option to safeguard their fertility. This group could include patients with recurrent endometriosis who are at a high risk of postoperative ovarian impairment or cases in which spontaneous conception is unlikely after ovarian surgery. On the other hand, the strengths, weaknesses, opportunities, and threats analysis concluded that the evidence of comparable results between IVF cycles conducted using vitrified versus fresh oocytes in other populations, such as oocyte donors, is one of the strengths of oocyte vitrification for FP in patients with endometriosis (53). Preserving oocytes at a young age, before the ovarian reserve is severely impacted, was discussed as one of the advantages of the approach among other aspects, whereas the psychological impact and lack of information regarding oocyte survival rates and IVF outcomes in patients with endometriosis were listed among the potential threats (53).

There are very few reports on the use of FP in endometriosis. A case report published in 2009 described a single 25-year-old woman with symptomatic endometriosis who underwent 4 surgical interventions, including unilateral oophorectomy, and COS before further treatment (54). Twenty-five mature oocytes were vitrified after 3 COS procedures. The patient has not yet returned to attempt pregnancy using her vitrified oocytes. A second publication, published in 2018, reported a retrospective analysis of 70 COS procedures performed on 49 patients with endometriosis to vitrify their oocytes for FP (55). They analyzed the data based on the presence of endometrioma, a history of cystectomy, and the presence of deep infiltrating endometriosis. The mean age of the patients was 33.9 ± 4.5 years, and the mean anti-müllerian hormone serum levels and antral follicle counts were 2.3 ± 1.8 ng/mL and 13.0 ± 10.4 follicles, respectively. The most remarkable finding of this report is that the parameters reflecting the number of oocytes retrieved and vitrified were significantly lower in patients reporting previous

TABLE 2

Cumulative live birth rate and 95% CI according to the number of oocytes used in each case of EFP, endo-FP, and onco-FP in patients aged ≤35 years (A) and >35 years (B).

A.

EFP n = 123		Endo-FP n = 260		Onco-FP n = 42	
No. of oocytes	**CLBR (95% CI)**	**No. of oocytes**	**CLBR (95% CI)**	**No. of oocytes**	**CLBR (95% CI)**
3	5.1 (0.7–9.4)	3	4.7 (2.3–7.2)		
5	15.8 (8.4–23.1)	5	11.5 (7.5–15.7)	5	9.1 (−0.7–19)
8	32.0 (22.1–41.9)	8	28.1 (22.0–34.3)	8	35.8 (14.3–57.2)
10	42.8 (31.7–53.9)	10	41.8 (34.7–48.9)	10	42.9 (19.7–66.1)
15	69.8 (57.4–82.2)	15	69.4 (61.4–77.4)	12	61.9 (35.4–88.5)
20	77.6 (64.4–90.9)	20	90.8 (80.4–101.2)		
24	94.4 (84.3–100.4)	22	95.4 (87.2–103.6)		

B.

EFP n = 518		Endo-FP n = 225		Onco-FP n = 38	
No. of oocytes	**CLBR (95% CI)**	**No. of oocytes**	**CLBR (95% CI)**	**No. of oocytes**	**CLBR (95% CI)**
3	5.9 (3.6–8.3)	3	4.8 (1.9–7.7)		
5	17.3 (13.3–21.3)	5	10.6 (6.4–15.0)	4	11.1 (−0.8–23.1)
8	17.3 (13.3–21.3)	8	18.7 (12.7–24.9)	9	29.3 (3.7–54.8)
10	25.2 (20.2–30.1)	10	24.3 (16.9–31.7)	10	43.4 (11.3–75.3)
15	38.8 (32.0–45.6)	15	46.9 (34.4–59.4)		
20	49.6 (40.7–58.4)	19	59.2 (43.4–75.2)		

Note: CI = confidence interval; CLBR = cumulative live birth rate; EFP = elective fertility preservation; endo-FP = fertility preservation in patients with endometriosis; onco-FP = oncological fertility preservation.

Cobo. FP results—elective and medical reasons. Fertil Steril 2021.

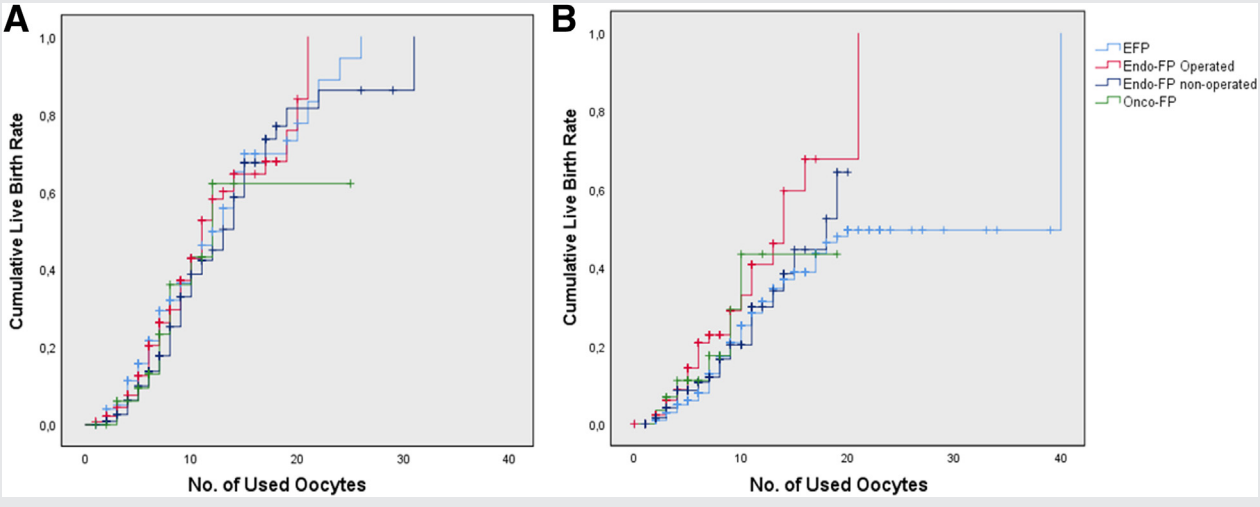
cystectomy when compared with those without ovarian surgery, which highlights the importance of preoperative FP counseling in young women with severe endometriosis (55).

A recent study (42) was very well received because it helped clarify the uncertainties related to the potential of vitrified oocytes for FP in patients with endometriosis and their reproductive chances with the approach and shed some light on factors related to success (56). The study included 485 women diagnosed with endometriosis who returned to use their oocytes after 1.7 ± 0.4 years of storage for FP and reported the birth of 225 healthy babies (42). A great majority (97.7%) of the patients had stages III–IV of the disease. These women were aged 35.7 ± 3.7 years at the time of oocyte retrieval; a mean of 9.4 ± 6.7 oocytes were retrieved, and 5.5 ± 5.2 MII oocytes were vitrified per patient and per cycle (mean vitrification cycles = 1.7 ± 1.1). These figures already reflect a compromise of the ovarian reserve when compared with that of healthy responders. The overall oocyte survival rate was 83.2%, but it was significantly lower when analyzed by age (85.1% in patients aged ≤ 35 years vs. 80.8% in patients aged >35 years, $P<.05$). Moreover, age (≤35 years vs 35 years) had a negative effect on not only this parameter but also the number of retrieved and vitrified oocytes, embryo quality, and clinical outcomes, including CLBR per patient (61.4% vs 28.4%). These findings were somewhat expected because age is one of the most powerful confounders in AR, and patients with endometriosis are no exception.

The study also addressed the issue of ovarian response and clinical outcomes in patients who have undergone cystectomy before opting for oocyte vitrification for FP. Perhaps the most remarkable finding of this study has to do with the effect of age in the surgical group: CLBR was significantly higher in young (≤35 years), nonoperated patients (72.5%) compared with that in age-matched operated ones (42.8%). So, perhaps the most useful observation in this study is that women diagnosed with endometrioma and a history of cystectomy at a young age should consider oocyte retrieval and FP before surgery. Figure 2 and Table 3 shows CLBR in 3 different populations according to age: EFP patients, oncological patients, and patient with endometriosis who underwent ovarian surgery before FP or not; it revealed that with the use of the same number of oocytes, the results were comparable in the young group, thus suggesting that the impact of surgery on the ovarian reserve is quantitative rather than qualitative. Similar findings are shown in the Figure 3 and Table 4, in which the group of surgical patients with endometriosis was subdivided based on whether the surgery was unilateral or bilateral.

Interestingly enough, that does not seem to be the trend in the clinical management of these patients. In the study we are currently referring to (42), most of the young women who came to the fertility center seeking FP had already been operated on somewhere else, indicating that the main priority when managing patients in need of surgical treatment for endometrioma is to go ahead with surgery, without considering oocyte retrieval for FP before the intervention, to forestall its adverse effect on the ovarian reserve. Thus, the worse reproductive prognosis observed in young surgical patients, despite their young age, is somewhat expected because of the compromise of the ovarian reserve in addition to the fact that oocyte quality is also likely to be compromised (57, 58).

FIGURE 2



Kaplan-Meier plot of cumulative probability of live birth for patients who underwent EFP (*blue*), endo-FP who underwent ovarian surgery to remove an endometrioma (*red*), endo-FP who did not undergo surgery (*dark blue*), and onco-FP (*green*) according to the number of oocytes used. Overall comparisons (log rank [Mantel-Cox], Breslow [generalized-Wilcoxon], and Tarone-Ware) showed no statistical differences for women aged ≤35 years (**A**) ($P = .752$, .556, and .675, respectively) and women aged >35 years (**B**) ($P = .029$, .065, and .053, respectively). EFP = elective fertility preservation; endo-FP = fertility preservation in patients with endometriosis; onco-FP = oncological fertility preservation.

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TABLE 3

Cumulative live birth rate and 95% CI according to the number of oocytes used in each case of EFP, endo-FP operated and nonoperated, and onco-FP in patients aged ≤35 years (A) and >35 years (B).

A.

EFP n = 123		Endo-FP operated n = 140		Endo-FP nonoperated n = 120		Onco-FP n = 42	
No. of oocytes	**CLBR (95% CI)**	**No. of oocytes**	**CLBR (95% CI)**	**No. of oocytes**	**CLBR (95% CI)**	**No. of oocytes**	**CLBR (95 %CI)**
3	5.1 (0.7–9.4)	3	3.7 (0.5–6.7)	4	4.5 (0.7–8.5)		
5	15.8 (8.4–23.1)	5	9.4 (4.3–14.4)	5	7.4 (2.5–12.3)	5	9.1 (−0.7–19)
8	32.0 (22.1–41.9)	8	26.9 (18.5–35.4)	8	23.1 (14.8–31.4)	8	35.8 (14.3–57.2)
10	42.8 (31.7–53.9)	10	40.7 (51.1–75.3)	10	36.9 (27.1–46.8)	10	42.9 (19.7–66.1)
15	69.8 (57.4–82.2)	14	63.2 (51.1–75.3)	15	66.5 (55.8–77.2)	12	61.9 (35.4–88.5)
20	77.6 (64.4–90.9)	20	83.3 (65.7–100.8)	19	80.9 (68.7–93.3)		
22–24	94.4 (84.3–100.4)		3.7 (0.5–6.7)	22	85.7 (73.5–97.9)		

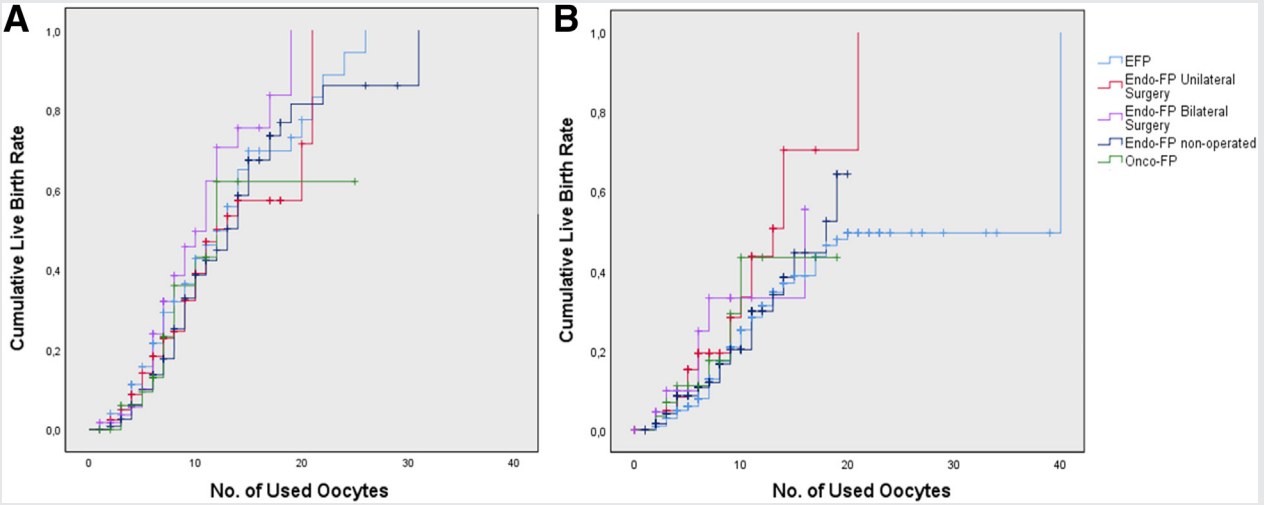
B.

EFP n = 518		Endo-FP operated n = 92		Endo-FP nonoperated n = 133		Onco-FP n = 38	
No. of oocytes	**CLBR (95% CI)**	**No. of oocytes**	**CLBR (95% CI)**	**No. of oocytes**	**CLBR (95% CI)**	**No. of oocytes**	**CLBR (95% CI)**
3	5.9 (3.6–8.3)	3	6.1 (0.9–11.2)	3	4.1 (0.6–7.7)	4	11.1 (−0.8–23.1)
5	17.3 (13.3–21.3)	5	14.3 (6.4–22.1)	6	10.7 (4.9–16.5)		
8	17.3 (13.3–21.3)	7	22.8 (12.7–32.8)	8	16.6 (8.8–24.4)	9	29.3 (3.7–54.8)
10	25.2 (20.2–30.1)	10	32.6 (19.0–46.8)	11	29.9 (18.1–41.7)	10	43.4 (11.3–75.3)
15	38.8 (32.0–45.6)	14	59.6 (38.7–80.5)	15	44.6 (26.7–62.4)		
20	49.6 (40.7–58.4)	16	67.7 (45.8–89.6)	19	64.4 (38.8–89.9)		

Note: CI = confidence interval; CLBR = cumulative live birth rate; EFP = elective fertility preservation; endo-FP = fertility preservation in patients with endometriosis; onco-FP = oncological fertility preservation.

Cobo. FP results—elective and medical reasons. Fertil Steril 2021.

FIGURE 3



Kaplan-Meier plot of cumulative probability of live birth for patients who underwent EFP (*blue*), endo-FP who underwent unilateral (*red*) or bilateral (*purple*) ovarian surgery to remove endometrioma, endo-FP who did not undergo surgery (*dark blue*), and onco-FP (*green*) according to the number of oocytes used. Overall comparisons (log rank [Mantel-Cox], Breslow [generalized-Wilcoxon], and Tarone-Ware) showed no statistical differences in women aged ≤35 years (**A**) (P = .331, .490, and .448, respectively) and women aged >35 years (**B**) (P = .059, .117, and .102, respectively). EFP = elective fertility preservation; endo-FP = fertility preservation in patients with endometriosis; onco-FP = oncological fertility preservation.

Cobo. FP results—elective and medical reasons. Fertil Steril 2021.

TABLE 4

Cumulative live birth rate and 95% CI according to the number of oocytes used in each case of EFP; endo-FP women who underwent unilateral or bilateral surgery or did not undergo surgery; and onco-FP in patients aged ≤35 years (A) and >35 years (B).

A.

EFP		Endo-FP unilateral surgery		Endo-FP bilateral surgery		Endo-FP nonoperated		Onco-FP	
n = 123		n = 83		n = 57		n = 120		n = 42	
No. of oocytes	CLBR (95% CI)	No. of oocytes	CLBR (95% CI)	No. of oocytes	CLBR (95% CI)	No. of oocytes	CLBR (95% CI)	No. of oocytes	CLBR (95% CI)
3	5.1 (0.7–9.4)	3	5.0 (0.2–9.7)	3	8.7 (1.3–8.7)	4	4.5 (0.7–8.5)		-
5	15.8 (8.4–23.1)	5	14.2 (6.4–21.9)	5	18.6 (1.7–18.6)	5	7.4 (2.5–12.3)	5	9.1 (−0.7–19)
8	32.0 (22.1–41.9)	8	24.6 (14.6–34.5)	8	53.9 (23.2–53.9)	8	23.1 (14.8–31.4)	8	35.8 (14.3–57.2)
10	42.8 (31.7–53.9)	10	39.1 (26.4–51.7)	10	66.6 (32.7–66.6)	10	36.9 (27.1–46.8)	10	42.9 (19.7–66.1)
15	69.8 (57.4–82.2)	14	57.4 (42.0–72.7)	14	92.3 (58.8–92.3)	15	66.5 (55.8–77.2)	12	61.9 (35.4–88.5)
20	77.6 (64.4–90.9)	20	71.6 (46.6–96.5)	17	100.9 (66.5–100.9)	19	80.9 (68.7–93.3)		-
22–24	94.4 (84.3–100.4)					22	85.7 (73.5–97.9)		-

B.

EFP		Endo-FP unilateral surgery		Endo-FP bilateral surgery		Endo-FP nonoperated		Onco-FP	
n = 518		n = 68		n = 24		n = 133		n = 38	
No. of oocytes	CLBR (95% CI)	No. of oocytes	CLBR (95% CI)	No. of oocytes	CLBR (95% CI)	No. of oocytes	CLBR (95% CI)	No. of oocytes	CLBR (95% CI)
3	5.9 (3.6–8.3)	3	4.8 (0.5–10.1)	3	9.8 (3.1–22.8)	4	4.5 (0.7–8.5)	4	11.1 (−0.8–23.1)
5	17.3 (13.3–21.3)	6	19.3 (8.9–29.7)	6	24.9 (3.0–46.8)	5	7.4 (2.5–12.3)		
8	17.3 (13.3–21.3)			7	33.2 (8.4–58.1)	8	23.1 (14.8–31.4)	9	29.3 (3.7–54.8)
10	25.2 (20.2–30.1)	10	33.4 (16.5–50.3)			10	36.9 (27.1–46.8)	10	43.4 (11.3–75.3)
15	38.8 (32.0–45.6)	14	70.4 (45.7–95.1)	16	55.4 (16.2–94.7)	15	66.5 (55.8–77.2)		
20	49.6 (40.7–58.4)					19	80.9 (68.7–93.3)		
						22	85.7 (73.5–97.9)		

Note: CI = confidence interval; CLBR = cumulative live birth rate; EFP = elective fertility preservation; endo-FP = fertility preservation in patients with endometriosis; onco-FP = oncological fertility preservation.

Cobo. FP results—elective and medical reasons. Fertil Steril 2021.

Additionally, evidence collected regarding patients undergoing EFP showed that the number of oocytes available in combination with age is closely related to CLBR (26). Therefore, if a patient with endometriosis, despite being young, yields few oocytes, lower success rates are expected. In addition, women diagnosed with endometriosis at a young age may have a greater risk of recurrence (59), and because they are not expected to seek motherhood in a short-to-medium term, advice on FP is strongly encouraged.

In patients aged >35 years, cystectomy had no effect on the success rates, suggesting tailored management in this group. According to the data published by Cobo et al. (42) in 2020, FP in older women might not be as effective, regardless of whether they underwent surgery. This contradicts other investigators who have recommended FP in poor-prognosis patients with endometriosis (20).

EFP FOR AGE-RELATED FERTILITY DECLINE

Elective FP has led to a revolution in not only the social domain but also the field of reproductive medicine because it has provided practitioners with the opportunity to offer improvement in the autonomy of many women in their decision to become mothers. In the modern society, many women are delaying pregnancy beyond the younger years of childbearing because of not only professional aspirations but also voluntary childlessness, which can be permanent or, as is more frequently observed, temporary. Unfortunately, sometimes, when women change their mind and decide to start trying to get pregnant, it is too late because the constant ticking of the biological clock inevitably leads to natural depletion of the ovarian reserve. There are numerous articles analyzing different aspects of EFP related to social and demographic characteristics, ethics, and motivations and perceptions of women who decide to electively safeguard their fertility for the future. One study analyzing the cost-effectiveness issues of the approach is also available (60). However, very few publications have reported results after the use of vitrified oocytes for age-related fertility decline, which is the scope of the current review.

To our knowledge, the first report providing clinical data, including live births after EFP using vitrified oocytes, was published in 2013 (34). The investigators described their experience of storing oocytes during a course of 5 years for EFP and patients with cancer (data on the latter has already been addressed in the present review). The EFP group included 560 women (mean age = 36.7 ± 4.2 years) who chose FP because of age-related fertility decline (90.6%). Among them, 20 patients returned to attempt pregnancy with their stored oocytes. The birth of 5 healthy babies was reported in this study. An update of this data was published in 2016, providing a detailed description of the investigators' EFP program, including the profile of the women who had vitrified oocytes for FP, the rate at which they returned to use their oocytes, their clinical outcomes, and the probability of having a baby according to the number of oocytes used (24). The study included 1,468 women, and most of them (n = 1,382) opted for EFP because of age-related fertility decline (social reasons). Most were highly educated and single heterosexual women. Among 137 women who returned to use their oocytes, 26 deliveries and 31 babies were reported. Most women decided on EFP at an advanced age: 16.2% were aged ≥40 years at the time of oocyte retrieval, whereas a minority was <30 years of age (1.9%) (24). As expected, a larger number of oocytes was either retrieved or vitrified in patients aged ≤35 years when compared with the older patients, and the lowest figures were observed in the group of the oldest patients aged ≥40 years. Age also negatively impacted the rates of oocyte survival (94.6% in those ≤35 years vs. 82.4% in those >35 years) and live births per patient (50% in those ≤35 years vs. 22.9% in those >35 years). Moreover, the study also showed that CLBR worsened dramatically after the age of 40 years (3.7%). As shown in Figure 1 and Table 2, the cumulative probability of having a child based on the number oocytes used per patient showed that 8–10 MII oocytes are needed to achieve reasonable success in women <35 years (24). The investigators also suggested that the numbers should be individualized in older women.

Another report also showed age-related estimates of oocytes leading to live-born children (39). The study group included EFP cycles as well as other autologous cycles conducted using vitrified oocytes for other reasons. These investigators suggested cryopreserving 15–20 oocytes for women <38 years of age to attain a 70%–80% probability of achieving at least one baby and 25–30 oocytes for women aged 38–40 years to reach a 65%–75% chance of at least one baby. These findings were very similar to those reported 1 year later in another study, in which after using 15–20 vitrified oocytes respectively per EFP patient, CLBR was 69.8% and 77.6% (26). The effect of age on CLBR was also shown in a later study by a Swedish center, which included data on 38 women out of 254 women who underwent EFP (return rate = 15%) (41). Cumulative live birth rates of 63%, 26%, and 0% in women aged 36–37, 38–39, and ≥40 years at the time of vitrification, respectively, were reported. The study reported a total of 5 babies.

The significantly higher efficiency of EFP in young women indicates that patients considering oocyte vitrification should be counseled to do it earlier; however, some debates have arisen regarding cost-effectiveness because some analyses have shown that egg banking for FP is more cost-effective in women <38 years (61, 62).

The joint effect of age and indication was also studied in 3 different populations (52). This analysis showed the outcomes achieved in oocyte donors, poor responders, and patients undergoing EFP according to 2 age groups (≤35 years vs. >35 years). The oocyte survival and clinical outcomes were worse in young poor responders when compared with those in donor and EFP age-matched groups. The assumption that donors and patients undergoing EFP are comparable groups is acceptable because they are both young healthy women. On the contrary, poor responders are infertile patients with a compromised ovarian reserve and high likelihood of having compromised oocyte quality, which can be responsible for the poorer outcome achieved in this group despite their young age. Further evidence of the relationship between the outcome

and indication for FP, e.g., endometriosis, was also shown, as discussed earlier in the present review (42).

CLOSING REMARKS

In conclusion, the efficiency of oocyte vitrification for safeguarding fertility is currently a consolidated option that can be offered as a way of forestalling age-related fertility decline to women at a risk of losing their ovarian function for medical reasons, such as patients with cancer or women diagnosed with endometriosis, and to women who wish to delay motherhood. Although evidence is still less, currently available studies show successful outcomes in these 3 populations. Nonetheless, the results depend on different variables:

- The age of the patient at the time of oocyte retrieval strongly affects outcomes in all the populations studied. Patients undergoing EFP and patients with endometriosis should be counseled to decide for FP at a young age ($\leq$35 years).
- The indication for FP can be related to the success rates because poorer outcomes are achieved in patients with endometriosis and cancer; however, the role of the disease in the latter is yet to be proven.
- In patients with endometriosis, surgical excision of the endometrioma before the collection of oocytes for FP strongly affects the outcome in younger patients. Therefore, they should be encouraged to have their oocytes vitrified before surgery.
- The number of oocytes available, in combination with age, strongly impacts the live birth rates, with a great increase in the outcome with few oocytes added, especially at a young age.
- It is desirable to have 10–15 oocytes available in patients aged $\leq$35 years to achieve reasonable success rates (CLBR of 40%–70%). This number of oocytes can be achieved in 1 or 2 COS procedures.

Finally, we think it is mandatory to explain to women with different indications who opt for FP that oocyte cryostorage is not an insurance policy to secure future motherhood but a means to increase their chances of having a biological child.

REFERENCES

1. Chen C. Pregnancy after human oocyte cryopreservation. Lancet 1986;1:884–6.
2. Kuleshova L, Gianaroli L, Magli C, Ferraretti A, Trounson A. Birth following vitrification of a small number of human oocytes: case report. Hum Reprod 1999;14:3077–9.
3. Cobo A, Diaz C. Clinical application of oocyte vitrification: a systematic review and meta-analysis of randomized controlled trials. Fertil Steril 2011;96:277–85.
4. Kuwayama M. Highly efficient vitrification for cryopreservation of human oocytes and embryos: the cryotop method. Theriogenology 2007;67:73–80.
5. Cobo A, Meseguer M, Remohi J, Pellicer A. Use of cryo-banked oocytes in an ovum donation programme: a prospective, randomized, controlled, clinical trial. Hum Reprod 2010;25:2239–46.
6. Cobo A, Garrido N, Pellicer A, Remohi J. Six years' experience in ovum donation using vitrified oocytes: report of cumulative outcomes, impact of storage time, and development of a predictive model for oocyte survival rate. Fertil Steril 2015;104:1426–34.e8.
7. Cobo A, Serra V, Garrido N, Olmo I, Pellicer A, Remohi J. Obstetric and perinatal outcome of babies born from vitrified oocytes. Fertil Steril 2014;102:1006–15.e4.
8. Noyes N, Porcu E, Borini A. Over 900 oocyte cryopreservation babies born with no apparent increase in congenital anomalies. Reprod Biomed Online 2009;18:769–76.
9. Setti PE, Albani E, Morenghi E, Morreale G, Delle Piane L, Scaravelli G, et al. Comparative analysis of fetal and neonatal outcomes of pregnancies from fresh and cryopreserved/thawed oocytes in the same group of patients. Fertil Steril 2013;100:396–401.
10. Greco E, Litwicka K, Arrivi C, Varricchio MT, Zavaglia D, Mencacci C, et al. Accumulation of oocytes from a few modified natural cycles to improve IVF results: a pilot study. J Assist Reprod Genet 2013;30:1465–70.
11. Milan M, Cobo AC, Rodrigo L, Mateu E, Mercader A, Buendia P, et al. Redefining advanced maternal age as an indication for preimplantation genetic screening. Reprod Biomed Online 2010;21:649–57.
12. Chamayou S, Sicali M, Alecci C, Ragolia C, Liprino A, Nibali D, et al. The accumulation of vitrified oocytes is a strategy to increase the number of euploid available blastocysts for transfer after preimplantation genetic testing. J Assist Reprod Genet 2017;34:479–86.
13. Herrero L, Pareja S, Losada C, Cobo AC, Pellicer A, Garcia-Velasco JA. Avoiding the use of human chorionic gonadotropin combined with oocyte vitrification and GnRH agonist triggering versus coasting: a new strategy to avoid ovarian hyperstimulation syndrome. Fertil Steril 2011;95:1137–1140.
14. Levi-Setti PE, Borini A, Patrizio P, Bolli S, Vigiliano V, De Luca R, et al. ART results with frozen oocytes: data from the Italian ART registry (2005–2013). J Assist Reprod Genet 2016;33:123–8.
15. Cobo A, Garcia-Velasco JA, Domingo J, Remohi J, Pellicer A. Is vitrification of oocytes useful for fertility preservation for age-related fertility decline and in cancer patients? Fertil Steril 2013;99:1485–95.
16. Diaz-Garcia C, Domingo J, Garcia-Velasco JA, Herraiz S, Mirabet V, Iniesta I, et al. Oocyte vitrification versus ovarian cortex transplantation in fertility preservation for adult women undergoing gonadotoxic treatments: a prospective cohort study. Fertil Steril 2018;109:478–85.e2.
17. Donnez J, Squifflet J, Jadoul P, Lousse JC, Dolmans MM, Donnez O. Fertility preservation in women with ovarian endometriosis. Front Biosci (Elite Ed.) 2012;4:1654–62.
18. Tomassetti C, D'Hooghe T. Endometriosis and infertility: insights into the causal link and management strategies. Best Pract Res Clin Obstet Gynaecol 2018;51:25–33.
19. Gupta S, Goldberg JM, Aziz N, Goldberg E, Krajcir N, Agarwal A. Pathogenic mechanisms in endometriosis-associated infertility. Fertil Steril 2008;90:247–57.
20. Somigliana E, Vigano P, Filippi F, Papaleo E, Benaglia L, Candiani M, et al. Fertility preservation in women with endometriosis: for all, for some, for none? Hum Reprod 2015;30:1280–6.
21. Garcia-Velasco JA, Somigliana E. Management of endometriomas in women requiring IVF: to touch or not to touch. Hum Reprod 2009;24:496–501.
22. Inhorn MC, Birenbaum-Carmeli D, Birger J, Westphal LM, Doyle J, Gleicher N, et al. Elective egg freezing and its underlying sociodemography: a binational analysis with global implications. Reprod Biol Endocrinol 2018;16:70.
23. Homburg R, van der Veen F, Silber SJ. Oocyte vitrification—women's emancipation set in stone. Fertil Steril 2008;91:1319–20.
24. Cobo A, Garcia-Velasco JA, Coello A, Domingo J, Pellicer A, Remohi J. Oocyte vitrification as an efficient option for elective fertility preservation. Fertil Steril 2016;105:755–64.e8.
25. Rienzi L, Gracia C, Maggiulli R, LaBarbera AR, Kaser DJ, Ubaldi FM, et al. Oocyte, embryo and blastocyst cryopreservation in ART: systematic review and meta-analysis comparing slow-freezing versus vitrification to produce evidence for the development of global guidance. Hum Reprod Update 2017;23:139–55.
26. Cobo A, Garcia-Velasco J, Domingo J, Pellicer A, Remohi J. Elective and onco-fertility preservation: factors related to IVF outcomes. Hum Reprod 2018;33:2222–31.

27. Yang D, Brown SE, Nguyen K, Reddy V, Brubaker C, Winslow KL. Live birth after the transfer of human embryos developed from cryopreserved oocytes harvested before cancer treatment. Fertil Steril 2007;87:1469.e1–4.
28. Porcu E, Venturoli S, Damiano G, Ciotti PM, Notarangelo L, Paradisi R, et al. Healthy twins delivered after oocyte cryopreservation and bilateral ovariectomy for ovarian cancer. Reprod Biomed Online 2008;17:265–7.
29. Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. Fertil Steril 2013;99:37–43.
30. Dondorp W, de Wert G, Pennings G, Shenfield F, Devroey P, Tarlatzis B, et al. Oocyte cryopreservation for age-related fertility loss. Hum Reprod 2012;27:1231–7.
31. Martinez F. Update on fertility preservation from the Barcelona International Society for Fertility Preservation-ESHRE-ASRM 2015 expert meeting: indications, results and future perspectives. Fertil Steril 2017;108:407–15.e11.
32. Sanchez-Serrano M, Crespo J, Mirabet V, Cobo AC, Escriba MJ, Simon C, et al. Twins born after transplantation of ovarian cortical tissue and oocyte vitrification. Fertil Steril 2010;93:268.e11–3.
33. Kim MK, Lee DR, Han JE, Kim YS, Lee WS, Won HJ, et al. Live birth with vitrified-warmed oocytes of a chronic myeloid leukemia patient nine years after allogenic bone marrow transplantation. J Assist Reprod Genet 2011;28:1167–70.
34. Garcia-Velasco JA, Domingo J, Cobo A, Martinez M, Carmona L, Pellicer A. Five years' experience using oocyte vitrification to preserve fertility for medical and nonmedical indications. Fertil Steril 2013;99:1994–9.
35. Alvarez M, Sole M, Devesa M, Fabregas R, Boada M, Tur R, et al. Live birth using vitrified–warmed oocytes in invasive ovarian cancer: case report and literature review. Reprod Biomed Online 2014;28:663–8.
36. da Motta EL, Bonavita M, Alegretti JR, Chehin M, Serafini P. Live birth after 6 years of oocyte vitrification in a survivor with breast cancer. J Assist Reprod Genet 2014;31:1397–400.
37. Martinez M, Rabadan S, Domingo J, Cobo A, Pellicer A, Garcia-Velasco JA. Obstetric outcome after oocyte vitrification and warming for fertility preservation in women with cancer. Reprod Biomed Online 2014;29:722–8.
38. Perrin J, Saias-Magnan J, Broussais F, Bouabdallah R, D'Ercole C, Courbiere B. First French live-birth after oocyte vitrification performed before chemotherapy for fertility preservation. J Assist Reprod Genet 2016;33:663–6.
39. Doyle JO, Richter KS, Lim J, Stillman RJ, Graham JR, Tucker MJ. Successful elective and medically indicated oocyte vitrification and warming for autologous in vitro fertilization, with predicted birth probabilities for fertility preservation according to number of cryopreserved oocytes and age at retrieval. Fertil Steril 2016;105:459–66.e2.
40. Specchia C, Baggiani A, Immediata V, Ronchetti C, Cesana A, Smeraldi A, et al. Oocyte cryopreservation in oncological patients: eighteen years experience of a tertiary care referral center. Front Endocrinol (Lausanne) 2019;10:600.
41. Wennberg AL, Schildauer K, Brannstrom M. Elective oocyte freezing for nonmedical reasons: a 6-year report on utilization and in vitro fertilization results from a Swedish center. Acta Obstet Gynecol Scand 2019;98:1429–34.
42. Cobo A, Giles J, Paolelli S, Pellicer A, Remohi J, Garcia-Velasco JA. Oocyte vitrification for fertility preservation in women with endometriosis: an observational study. Fertil Steril 2020;113:836–44.
43. Oktay K. Further evidence on the safety and success of ovarian stimulation with letrozole and tamoxifen in breast cancer patients undergoing in vitro fertilization to cryopreserve their embryos for fertility preservation. J Clin Oncol 2005;23:3858–9.
44. Cardozo ER, Thomson AP, Karmon AE, Dickinson KA, Wright DL, Sabatini ME. Ovarian stimulation and in-vitro fertilization outcomes of cancer patients undergoing fertility preservation compared to age matched controls: a 17-year experience. J Assist Reprod Genet 2015;32:587–96.
45. Dolinko AV, Farland LV, Missmer SA, Srouji SS, Racowsky C, Ginsburg ES. Responses to fertility treatment among patients with cancer: a retrospective cohort study. Fertil Res Pract 2018;4:3.
46. Quinn MM, Cakmak H, Letourneau JM, Cedars MI, Rosen MP. Response to ovarian stimulation is not impacted by a breast cancer diagnosis. Hum Reprod 2017;32:568–74.
47. Tsampras N, Gould D, Fitzgerald CT. Double ovarian stimulation (DuoStim) protocol for fertility preservation in female oncology patients. Hum Fertil 2017;20:248–53.
48. Friedler S, Koc O, Gidoni Y, Raziel A, Ron-El R. Ovarian response to stimulation for fertility preservation in women with malignant disease: a systematic review and meta-analysis. Fertil Steril 2012;97:125–33.
49. von Wolff M, Bruckner T, Strowitzki T, Germeyer A. Fertility preservation: ovarian response to freeze oocytes is not affected by different malignant diseases—an analysis of 992 stimulations. J Assist Reprod Genet 2018;35:1713–9.
50. Oktay K, Kim JY, Barad D, Babayev SN. Association of *BRCA1* mutations with occult primary ovarian insufficiency: a possible explanation for the link between infertility and breast/ovarian cancer risks. J Clin Oncol 2010;28:240–4.
51. Lambertini M, Goldrat O, Ferreira AR, Dechene J, Azim HA Jr, Desir J, et al. Reproductive potential and performance of fertility preservation strategies in *BRCA*-mutated breast cancer patients. Ann Oncol 2018;29:237–43.
52. Niederberger C, Pellicer A, Cohen J, Gardner DK, Palermo GD, O'Neill CL, et al. Forty years of IVF. Fertil Steril 2018;110:185–324.e5.
53. Streuli I, Benard J, Hugon-Rodin J, Chapron C, Santulli P, Pluchino N. Shedding light on the fertility preservation debate in women with endometriosis: a SWOT analysis. Eur J Obstet Gynecol Reprod Biol 2018;229:172–8.
54. Elizur SE, Chian RC, Holzer HE, Gidoni Y, Tulandi T, Tan SL. Cryopreservation of oocytes in a young woman with severe and symptomatic endometriosis: a new indication for fertility preservation. Fertil Steril 2009;91:293.e1–3.
55. Raad J, Sonigo C, Tran C, Sifer C, Durnerin IC, Grynberg M. Oocyte vitrification for preserving fertility in patients with endometriosis: first observational cohort study... and many unresolved questions [letter]. Eur J Obstet Gynecol Reprod Biol 2018;220:140–1.
56. Somigliana E, Vercellini P. Fertility preservation in women with endometriosis: speculations are finally over, the time for real data is initiated. Fertil Steril 2020;113:765–6.
57. Sanchez AM, Vanni VS, Bartiromo L, Papaleo E, Zilberberg E, Candiani M, et al. Is the oocyte quality affected by endometriosis? A review of the literature. J Ovarian Res 2017;10:43.
58. Ferrero H, Corachan A, Aguilar A, Quinonero A, Carbajo-Garcia MC, Alama P, et al. Single-cell RNA sequencing of oocytes from ovarian endometriosis patients reveals a differential transcriptomic profile associated with lower quality. Hum Reprod 2019;34:1302–12.
59. Brosens I, Gordts S, Benagiano G. Endometriosis in adolescents is a hidden, progressive and severe disease that deserves attention, not just compassion. Hum Reprod 2013;28:2026–31.
60. van Loendersloot LL, Moolenaar LM, Mol BW, Repping S, van der Veen F, Goddijn M. Expanding reproductive lifespan: a cost-effectiveness study on oocyte freezing. Hum Reprod 2011;26:3054–60.
61. Mesen TB, Mersereau JE, Kane JB, Steiner AZ. Optimal timing for elective egg freezing. Fertil Steril 2015;103:1551–6.e1–e4.
62. Waldby C. 'Banking time': egg freezing and the negotiation of future fertility. Cult Health Sex 2015;17:470–82.