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Number needed to freeze: cumulative live birth rate after fertility preservation in women with endometriosis

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Abstract

Research question: How does the number of oocytes used affect the cumulative live birth rate in endometriosis patients who had their oocytes vitrified for fertility preservation (FP)?

Design: Retrospective observational study including data from 485 women with endometriosis who underwent FP from January 2007 to July 2018. Survival curves and Kaplan-Meier plots were used to analyse the cumulative live birth rate (CLBR) according to the number of vitrified oocytes used. Data were stratified according to age, stage of the disease and ovarian surgery prior to FP (operated vs. non-operated). Endometriosis curves were compared to plots developed using elective fertility preservation (EFP) patients as control group. Log-rank, Breslow and Tarone-Ware tests were used to compare the survival curves.

Results: The CLBR increased as the number of oocytes used per patient rose, reaching 89.5% (95% CI=80.0-99.1) using 22 oocytes. Higher outcomes were observed in young women (≤35 y. vs. >35 y). In the younger group, the CLBR was 95.4% (95% CI=87.2-103.6) using ~20 oocytes vs. 79.6% (95% CI=58.1-101.1) in older women (P<0.05). No statistical differences were observed in overall calculations and according to age when the CLBR was compared between operated and non-operated women (NS). Comparable outcomes were also observed in stages I-II vs. III-IV (NS). The mean age was higher in EFP patients (37.2 ± 4.9 vs. 35.7 ± 3.7; P<0.05). The outcome was better in the endometriosis group as compared to EFP (P<0.05): a CLBR of 89.5% (80.0-99.1) vs. 59.9% (51.4-68.6) when 22 oocytes were used (P<0.05). However, the difference was milder when fewer oocytes were used in both groups. When comparisons were made between age-matching groups, no statistical differences were observed (NS).

Conclusion: The probability of live birth increases as the number of oocytes used rises in patients with endometriosis, but better outcomes were observed among young women. Neither the stage of the disease nor prior surgical excision of ovarian endometrioma were related to success. No statistical differences in age matching groups were observed when comparing to EFP patients. The information provided herein may be of interest to both patients and treating physicians for counselling purposes.

Key words

Endometriosis, fertility preservation, cystectomy, oocyte vitrification, cumulative live birth

Key message

The probability of live birth increases as the number of oocytes used rises in endometriosis, but better outcomes were observed in young women. Neither the stage of the disease nor ovarian surgery was associated with success. No statistical differences in age matching groups were observed when comparing to EFP patients.

Introduction

Fertility preservation (FP) is indicated in cases where the ovarian reserve, and thus the reproductive capacity, is jeopardized (Chapron *et al.*, 2019; Zondervan *et al.*, 2020). Oocyte vitrification has made the development of efficient FP programs possible, providing increasing evidence of successful practice over a decade (Cobo *et al.*, 2018). There are many situations in which women are at risk of significant loss in the follicle reserve, leading to a large population that can benefit from FP. Although this strategy was not initially conceived for elective purposes, its application seems reasonable when reproductive capacity is threatened by age-related fertility decline (Stoop *et al.*, 2014). For a variety of reasons, the number of women who voluntarily choose to postpone motherhood is increasingly growing, and more and more of them are opting for FP. Due to the nature of women's motivations and to the fact that they decide on their own to delay pregnancy beyond young childbearing years, this strategy is commonly known as elective fertility preservation (EFP) (Cobo and García-Velasco, 2016). Although the use of EFP has grown exponentially in recent years (Cobo *et al.*, 2018), the FP strategy was originally intended for women who needed to receive some form of treatment that might cause iatrogenic infertility.

Endometriosis, one of the most frequent pathologies in gynaecology, can also result in a considerable loss of ovarian reserve due to the progress of the disease or to the need for ovarian surgery (Donnez *et al.*, 2012;

Garcia-Velasco; Somigliana, 2009). Although FP is increasingly considered in patients with endometriosis, a generalized use still remains controversial (Somigliana *et al.*, 2015; Streuli *et al.*, 2018). Main concerns relate to the lack of evidence regarding the efficiency of FP in this specific population and the lack of knowledge regarding the quality of the vitrified oocytes and their ability to generate viable pregnancies in this group of women, all this added to the absence of cost-effectiveness studies (Somigliana *et al.*, 2015). We recently published a large study including women diagnosed with endometriosis who had their oocytes vitrified for FP and returned to attempt pregnancy (Cobo *et al.*, 2020). The study confirmed the usefulness of FP in managing future fertility expectations in endometriosis patients, showing efficient oocyte survival and clinical results after vitrification.

During counselling for FP there is a frequent question regarding the number of oocytes that need to be vitrified in order to increase future chances of success. We previously calculated the cumulative probability of achieving at least one live birth according to women's age and the number of oocytes used by EFP and cancer patients (Cobo *et al.*, 2018). This information is currently non-existent in the case of endometriosis patients, where the question becomes even more relevant because these women are at a greater risk of premature depletion of the ovarian reserve. The aim of the current study is to calculate the cumulative probability of achieving at least one live birth according to the number of oocytes used in patients with endometriosis. This figure refers to the number of oocytes warmed up by a patient in order to attempt pregnancy, including those oocytes that fail to survive, to fertilize or to develop into competent embryos. The impact of age at oocyte retrieval and surgical cystectomy is also analysed.

Materials and Methods

A retrospective study including 485 patients with endometriosis who had their oocytes vitrified for fertility preservation from January 2007 to July 2018 at IVIRMA clinics in Spain and returned to attempt pregnancy. Institutional Review Board approval was obtained (1710-VLC-100-AC). Data were collected from computerized clinical charts and remained anonymous in accordance with the Spanish law on assisted reproduction (Biomedical Research Law 14/2007).

Baseline characteristics and overall clinical outcomes when women attempted pregnancy with their vitrified-warmed oocytes were provided (Cobo *et al.*, 2020). The inclusion criteria for fertility preservation were: age up to 42 y., endometrioma larger than 1 cm in mean diameter with apparently healthy ovarian tissue (antral follicles) visible in the 2D ultrasound, and AMH >0.5 ng/ml and >3 antral follicles. The mean age at oocyte retrieval i.e. the age at vitrification for FP was 35.7 ± 3.7 y. Two hundred and sixty patients

were aged ≤35 y., (mean age=32.3 ± 2.6) while the remaining 225 were older than 35 (mean age=38.3 ± 1.9). The mean age when these women returned to attempt pregnancy was 37.3 ± 2.1 y. Stages I-II of endometriosis were diagnosed by laparoscopy, while deep infiltrating stages III-IV were confirmed by ultrasound in non-surgical patients. In addition, in operated patients, stage III-IV diagnosis was confirmed in the surgical report. The great majority of patients (N=474, 97.7%) were diagnosed with stage III-IV endometriosis. The mean age was comparable between patients diagnosed with I-II vs. III-IV stages (35.9 ± 3.7 vs. 35.0 ± 3.8 y. respectively) (NS). Two hundred and thirty-two patients (47.8%) opted for FP after having their endometrioma surgically removed elsewhere. Operated women were younger (mean age=33.4 ± 3.6) than non-surgically treated patients (mean age=36.7 ± 3.7) (P<0.05). Among them, 34.9% (N=81) underwent bilateral ovarian endometriotic cystectomy, while the remaining 65.1% (N=151) underwent unilateral surgery. Women submitted to bilateral surgery were younger than women treated with unilateral excision of endometrioma (mean age=33.4 ± 2.3 y. vs. 34.7 ± 2.7 y.; P<0,05).

The antagonist and agonist protocols used for ovarian stimulation (Cobo *et al.*, 2018), the Cryotop method for vitrification and warming of oocytes/embryos (Kitazato®, Shizuoka, Japan) (Coello *et al.*, 2016) and the endometrial preparation protocols have been described elsewhere (Cobo *et al.*, 2016; Soares *et al.*, 2005). 62 patients out of 485 (12.8%) needed PGT-A due to advanced maternal age. In all, 117 (22%) embryo transfers were cancelled due to: absence of chromosomally normal embryos (9.8%), absence of viable embryos (4.7%), fertilization failure (4.0%), deferred embryo transfer (2.3%) and oocyte survival failure (1.3%). A total of 225 babies were born (overall CLBR/patient=46.4%).

In order to allow the comparison of the CLBR achieved by FP patients with endometriosis versus patients not affected by the disease, a control group of elective fertility preservation (EFP) patients (N=641) from a study performed by Cobo et al. (Cobo *et al.*, 2018) was considered (Supplemental table 1). Women in the EFP group were older than the FP patients diagnosed with endometriosis (37.2 ± 4.9 vs. 35.5 ± 3.7 y.; P<0.05). 123 EFP patients were 35 years old or younger at the time of FP (mean age 32.6 ± 5.7), whereas most (N=528) were over 35 years of age (mean age=38.7 ± 2.8) (P<0.05). Due to advanced maternal age, a total of 228 patients (35.5%) needed PGT-A. Consequently, a high percentage of embryo transfer cancellation was observed in this group, mostly due to the presence of chromosomally abnormal embryos (46,8%).

Definition of outcomes and statistics

The primary outcome measure was the CLBR according to the number of oocytes used.

The cumulative probability of having at least one baby according to the total number of oocytes used in consecutive attempts was estimated using the Kaplan-Meier method, as previously described (Cobo *et al.*, 2016). The analysis comprised all the vitrification/warming cycles and the subsequent ICSI procedures undergone by a patient in order to attempt pregnancy and live birth after FP. All the procedures performed per patient were contemplated, including those that resulted in an embryo transfer as well as those where the embryo transfer was cancelled. Data from both fresh and frozen embryo transfers were included and computed until at least one live birth was achieved. In those cases where the same woman had more than one baby, only the first baby was considered; additional babies were excluded from the analysis, but data on the total number of babies achieved per patient is also provided in a separate analysis. In order to consider all the oocytes used to attempt a live birth in the Kaplan-Meier plotting, all women who returned to have their stored oocytes warmed-up were included in this analysis, even if they didn't get pregnant using their oocytes. We considered “oocytes used” to be all the oocytes that survived or did not survive the vitrification process; those that fertilised and those that did not; those that evolved into usable embryos (transferred or frozen) and those that, on the contrary, arrested in culture. Any embryos that were still cryopreserved at the time of the analysis were excluded. The analysis was performed on the whole endometriosis FP group. Additionally, data were stratified according to age, stage of the disease and ovarian surgery prior to FP. Endometriosis curves were compared to plots developed using elective fertility preservation (EFP) patients as a historical control group (Cobo *et al.*, 2018). Log-rank, Breslow and Tarone-Ware tests were used to compare the survival curves.

Results

Supplementary figure 1 shows the Kaplan-Meier plotting for the overall CLBR of our cohort. The table below the figure shows the CLBR when 3 to 22 oocytes were used. As shown by the curve, the CLBR increased as the number of oocytes used increased. With only 3 oocytes used, the CLBR was below 5%, but increased more than double to 11.2% (95% CI=8.2-14.2) when only two oocytes were added (from 3 to 5 oocytes). This implies a 3.6% increase per additional oocyte. By adding three more oocytes (from 5 to 8 oocytes used), the outcome increased to 24.4% (95% CI=8.2-14.2), representing a gain of 4.4% per additional oocyte. The increase per additional oocyte when 10 oocytes were used was 5.5% (CLBR=35.5; 95% CI=29.9-40.7). When the number of oocytes used reached 22, the CLBR was 89.5% (95% CI=80.0-99.1).

Figure 1 shows the CLBR according to the number of oocytes used categorized by age at oocyte retrieval i.e. age at vitrification for FP (≤35 y. vs. >35 y.). Statistical differences were observed between the two age

groups (P<0.05) using the same number of oocytes, but the differences were more noticeable from five oocytes onwards. Accordingly, when three more oocytes were added (from 5 to 8), the CLBR rose from 11.5% (95% CI=7.5-15.7) to 28.1% (95% CI=22.0-34.3), implying a gain of 5.5% per additional oocyte in patients aged ≤35 y. On the other hand, when the same number of oocytes was used in the group of patients aged >35 y., the outcome increased from 10.6% (95% CI=6.4-15.0) to 18.7% (95% CI=12.7-24.9), providing a gain of 2.7% per additional oocyte used (P<0.05). The gain per additional oocyte was higher all along the curve for patients aged ≤35 y. when compared to the >35 y. group. Similarly, the curves and the data tabulated in figure 2 show that when women from both groups of age used the same number of oocytes, the outcome was lower in older patients, i.e., with 10 oocytes the CLBR achieved was 41.8% vs 24.3%, respectively (P<0.05). In the younger group, the plateau was reached at a very high 95.4% outcome (95% CI=87.2-103.6) when 22 oocytes were used while, after using approximately the same number of oocytes, the CLBR was 79.6% (95%CI=58.1-101.1) in women older than 35 y. (P<0.05). Figure 2 shows the CLBR plots for patients that had surgery to remove ovarian endometriomas prior to FP, as well the results for patients who did not have surgical treatment, for both women aged 35 or younger (Panel A) and women above 35 (Panel B). No statistical differences were observed (NS). The overall CLBR stratified by surgery or no surgery, irrespectively of age, showed no statistical differences (NS) (data not shown). Similarly, supplementary figure 2, showing the results according to the stage of endometriosis, shows no statistical differences.

The CLBR according to the number of oocytes used by endometriosis versus EFP patients according to age is shown in supplementary figure 3. No statistical differences were observed in age matching groups, indeed, the curves practically overlapped (figure 3) for both endometriosis and EFP patients when aged ≤35 y. Additionally, the 95% confidence intervals showed no statistical differences throughout the curve (NS). Likewise, the CLBR for endometriosis and EFP patients above 35 years of age were comparable (NS). The total number of babies achieved per patient based on the number of oocytes used is shown in table 1. Although higher results were observed in EFP patients for some ranges of oocytes used, the differences did not reach significant values.

Discussion

Fertility preservation is increasingly considered an alternative for patients diagnosed with endometriosis who are at risk of compromised ovarian reserve. The usefulness of oocyte vitrification for FP in women with endometriosis was recently demonstrated in a large study which also confirmed the impact of age, number

of oocytes and egg survival on the cumulative live birth rate (Cobo *et al.*, 2020). Furthermore, the study showed that young women achieved better outcomes when they had oocytes vitrified for FP prior to the excision of ovarian endometrioma. The number of oocytes retrieved, therefore the number of metaphase II (MII) available for vitrification, was lower in operated women (Cobo *et al.*, 2020). The recognition of number of oocytes stored and patient age as key factors for success brings forth the question regarding the appropriate number of oocytes to vitrify. This question becomes even more relevant in endometriosis patients, since an already compromised ovarian reserve can be made worse if the patient has ovarian surgery. Furthermore, besides number, it is necessary to pay special attention to oocytes in endometriosis patients, since the existing evidence suggests that the outcome after ART relies on the quality of the oocytes rather than on altered endometrial receptivity (Garcia-Velasco *et al.*, 2015; Hauzman *et al.*, 2013). In addition, earlier studies published during the 1990's using the egg donation model showed that when oocytes from women with endometriosis were transferred to a healthy recipient, poorer outcomes were achieved, and when oocytes from healthy donors were allocated to affected recipients, the outcomes observed were similar to those of not affected recipients (Pellicer A, 1994; Simon *et al.*, 1994). A very recent study using single-cell RNA sequencing is consistent with earlier evidence, showing altered transcriptomics in oocytes from ovaries affected by endometriosis (Ferrero *et al.*, 2019).

In the present study we have analysed the cumulative probability of achieving at least one live birth (CLBR) in patients with endometriosis according to the total number of MII oocytes used, considering age and surgery as proven factors affecting the final outcome (Cobo *et al.*, 2020). As expected, the CLBR increased as the number of oocytes used rose and, not surprisingly, success rates were higher for young patients when compared to patients over 35. Therefore, the gain in yield (CLBR) per additional oocyte was very high practically throughout the entire curve, especially among young patients, revealing the advantage of adding very few more oocytes in this group. In contrast, in women aged more than 35 y., the gain in live birth yield was also noticeable but much lower, i.e., at some point of the curve from 5 to 8 oocytes the gain in young women doubles that in older women (5.5% vs. 2.7%). Additionally, young women reached a 95% success rate when approximately ~20 oocytes were used, while the maximum CLBR was set close to 80% when older women used similar numbers. These findings clearly indicate the beneficial effect of young age on reproductive outcomes; however, in our opinion, special attention must be paid when dealing with women with endometriosis, especially with those who required surgical treatment. While it is true that obtaining a maximum number of 15-20 oocytes to vitrify—probably in two stimulation cycles—is relatively easy in young women, this can be harder in a patient with endometriosis who, depending on the stage of the

disease, may already present a compromised ovarian reserve, which may have been made worse if the patient has undergone surgery. Consequently, even in young patients, several cycles might be needed in order to gather a suitable number of oocytes to help increase the chances of success (Carrillo *et al.*, 2016). Being aware of this is considerably helpful when it comes to offering a realistic scenario to women planning future motherhood, since it helps to avoid unrealistic expectations and encourages decision-making based on data.

We also found comparable results when plotting data according to the stage of endometriosis, but we cannot draw definitive conclusions from this analysis, since the number of patients in stages I-II is very low in our sample. However, we think that this finding will be confirmed, since there is no clear evidence of altered oocyte quality related to the progression of the disease (Diaz *et al.*, 2000; Sanchez *et al.*, 2017). Therefore, with the same number of oocytes used, we should expect comparable results regardless of the stage of the disease.

Similarly, we did not find differences in the CLBR between operated versus non-operated patients in age-matching groups. At first glance, this may appear contradictory but, in our opinion, these results are totally expectable and can be explained by the similar oocyte quality that can be anticipated in the same age group. Certainly, there is evidence of surgery-related damage to the ovarian reserve (Muzii *et al.*, 2014; Raffi *et al.*, 2012; Somigliana *et al.*, 2012). Nonetheless, these studies suggest a quantitative—not qualitative—effect of surgery on the ovarian reserve, leading to impaired IVF/ART outcomes (Benschop *et al.*, 2010; Hamdan *et al.*, 2015). We previously showed poorer results in surgically treated young women (Cobo *et al.*, 2020), but this impairment is due to the lower number of oocytes retrieved after surgery, which diminishes the chance of achieving pregnancy. In the present study, for the same number of oocytes used, the results are comparable regardless of whether the patient had previously had ovarian surgery or not.

In order to analyse the effect of the disease on the CLBR, we compared the plotting derived from endometriosis patients with that of patients doing elective fertility preservation (EFP) due to age-related fertility decline (figure 3).

Expectable statistical differences appeared between young and older groups considering the age at oocyte retrieval when the oocytes were vitrified for FP. When the comparison was made in age matching groups, the results were comparable for young (≤35 y.) and older women (>35 y.). This observation deserves special attention, since, if oocyte quality were compromised by endometriosis, it would lead us to expect differences at least in the young groups, given that the EFP patients are theoretically young healthy women.

However, it was not the case. It is worth mentioning that the Kaplan-Meier analysis used in our study calculates the probability of achieving at least one baby; hence, we calculated the total number of live births per patient according to the number of oocytes. The results were somewhat higher in the EFP group, but the differences did not reach significant values, thereby failing to confirm impaired outcomes in the young endometriosis patients. This could be due to different reasons. Firstly, our sample of EFP women aged ≤35 y. is half the size of the same-age endometriosis group. Secondly, age may be the main limiting factor, thus relegating the possible role of oocyte quality in the endometriosis group. This would also explain the fact that in older patients the results are likewise comparable, indicating that the variable that most disturbs the result is indeed age, as we demonstrated in our previous study (Cobo *et al.*, 2020). Age was also confirmed as the most powerful confounder in other FP populations, such as oncological patients (Cobo *et al.*, 2018). Thirdly, endometriosis affects fertility through several mechanisms, but the role of compromised oocyte quality and its impact on the reproductive outcome remains controversial (Gazvani; Templeton, 2002; Horton *et al.*, 2019; Young *et al.*, 2013). Existing publications analysing oocyte quality in patients with endometriosis show alterations in oocyte morphology, spindle abnormalities, lower mitochondrial content, alterations in the granulosa cells including dysregulations in steroidogenesis and increase in oxidative stress in the follicular fluid (Sanchez *et al.*, 2017) and a different transcriptomic profile associated with lower quality in oocytes from women with endometriosis (Ferrero *et al.*, 2019). Indeed, this could explain the lower survival rate and clinical outcome observed previously (Cobo *et al.*, 2020). Nonetheless, in the current study, when the analysis considers the same number of oocytes used, the CLBR becomes comparable between endometriosis patients and EFP controls. Additionally, different meta-analyses reporting parameters directly related to oocyte quality, such as the ability to complete maturation and the fertilization rate, have shown altered results in endometriosis patients versus controls (Barnhart *et al.*, 2002; Harb *et al.*, 2013). Other authors also reported similar pregnancy, live birth and miscarriage rates when comparing between endometriosis and other reasons for infertility (Gonzalez-Comadran *et al.*, 2017) and even when comparing stage III-IV with stage-I-II endometriosis (Barbosa *et al.*, 2014). Finally, we should also consider the possibility of unstudied subfertility in the EFP group or even the presence of undiagnosed stages I-II of endometriosis due to the need of laparoscopy for such diagnosis which is highly unlikely in a healthy woman seeking for fertility preservation.

Our study certainly has some limitations, especially related to the small sample that is left in some groups when we make subcategories by age or stage of the disease, thus making difficult to draw definitive conclusions from these analyses, highlighting the need for further studies including larger sample size. Even

so, we believe that the information provided herein may be of interest to both patients and treating physicians in relation to the necessary number of oocytes to vitrify to ensure a modicum of success. Fertility preservation is a key consideration in the care of young girls and women with endometriosis, mainly those with ovarian endometriomas and advanced disease, so we consider the dissemination of the results provided by this strategy of importance to define actions and relate them to the probability of success. This may help fertility specialists to adequately counsel their endometriosis patients, setting realistic expectations regarding what they may accomplish once the time comes to use their frozen oocytes.

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Table 1. Total live births per patient according to both age and the number of oocytes used per endometriosis/EFP patient.

No. of oocytes	ENDO ≤35 No. of patients	ENDO ≤35 Live births/patient (%)	EFP ≤35 No. of patients	EFP ≤35 Live births/patient (%)	P value
<5	50	30.0	20	55.0	0.051
5-10	125	65.6	46	69.6	0.626
>10-<15	46	87.0	19	89.5	0.778
≥15	36	61.1	15	80.0	0.192
	ENDO >35		**EFP >35**		
<5	62	24.2	61	27.9	0.642
5-10	112	17.9	220	29.5	0.021
>10-<15	35	34.3	73	31.5	0.773
≥15	19	15.8	58	15.5	0.974