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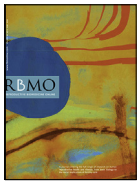

ARTICLE

Oocyte cryopreservation for fertility preservation in women with ovarian endometriosis

BIOGRAPHY

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KEY MESSAGE

Women with endometrioma are at a higher risk of decreased ovarian reserve and are potential candidates for fertility preservation. In women with endometrioma, oocyte cryopreservation before ovarian cystectomy could be a feasible option for fertility preservation.

ABSTRACT

Research-question: What is the clinical usefulness of oocyte cryopreservation for fertility preservation in women with ovarian endometriosis?

Design: Clinical characteristics were retrospectively analysed in 34 women with endometrioma before a planned ovarian cystectomy. Ovarian stimulation outcomes were compared according to laterality. A one-to-one propensity score-matched analysis was conducted to compare ovarian stimulation outcomes of the first cycle in patients with endometrioma undergoing fertility preservation with those in infertile patients without endometrioma who underwent IVF treatment. The number of oocytes cryopreserved in repeated ovarian stimulation cycles was analysed.

Results: The mean endometrioma size at diagnosis was 6.0 ± 2.5 cm. The mean age, serum anti-Mullerian hormone levels and number of oocytes cryopreserved were 30.7 ± 5.9 years, 1.85 ± 1.14 ng/ml, and 4.8 ± 3.2, respectively. The number of oocytes cryopreserved in bilateral endometrioma compared with unilateral endometrioma patients was 4.1 ± 2.9 versus 5.7 ± 3.4 ($P = 0.600$). In the propensity score-matched cohort ($n = 22$ per group), the number of oocytes retrieved was significantly lower in the patients with endometrioma undergoing fertility preservation compared with that in infertile patients without endometrioma (5.4 ± 3.8 versus 8.1 ± 4.8; $P = 0.045$). A total of 13 (38.2%) patients with endometrioma underwent repeated stimulation. The median (interquartile range) number of cryopreserved oocytes at the first and the second cycle were 3.0 (2.5–6.0) and 5.0 (2.5–7.5), respectively.

Conclusions: Women with endometrioma should be counselled about oocyte cryopreservation for fertility preservation before surgery. The number of cryopreserved oocytes can be increased by repeated oocyte retrieval.

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KEYWORDS

Endometriosis
Fertility preservation
Oocyte cryopreservation, Ovarian reserve
Vitrification

INTRODUCTION

Endometriosis has been shown to affect 6–10% of women of childbearing age; 35–50% of these women present with pain, infertility or both (*Giudice, 2010*). Endometriosis presents as an ovarian endometrioma in 17–44% of patients (*Redwine, 1999*; *Busacca and Vignali, 2003*). Endometriosis causes various symptoms, including dysmenorrhoea, dyspareunia, chronic pelvic pain and infertility (*Rice, 2002*). Women with endometriosis tend to have a lower monthly fecundity of about 0.02–0.1 per month than that in normal couples, which is 0.15–0.20 per month (*Schwartz and Mayaux, 1982*; *Hughes et al., 1993*). Several mechanisms explain the relationship between endometriosis and infertility: distorted pelvic anatomy, endocrine and ovulatory abnormalities, and altered peritoneal, hormonal and cell-mediated functions in the endometrium (*Bulletti et al., 2010*).

Ovarian endometriosis (endometrioma) itself reduces the ovarian reserve by affecting ovarian physiology in the healthy ovarian tissue surrounding it (*Sanchez et al., 2014*). Endometriomas contain fluid with excessive amounts of free iron, reactive oxygen species, proteolytic enzymes and inflammatory molecules, which lead to the substitution of normal ovarian cortical tissue with fibrous tissue followed by follicular loss (*Sanchez et al., 2014*). Clinically, women with endometrioma have lower anti-Müllerian hormone (AMH) levels and antral follicle counts, and therefore require higher doses of gonadotrophin than women without endometrioma (*Carrillo et al., 2016*).

The treatment for endometrioma is ovarian cystectomy in most cases. Ovarian cystectomy, however, has been associated with a risk of premature ovarian failure. Postoperative ovarian failure rates have been reported as 2.4–13% (*Busacca et al., 2006*; *Benaglia et al., 2010*). Recently, many studies, including meta-analyses, have shown that the ovarian reserve represented by AMH levels decreases after surgery (*Chang et al., 2010*; *Raffi et al., 2012*; *Somigliana et al., 2012*). Several mechanisms have been presented to explain the reduction in ovarian reserve resulting from cystectomy: excessive removal of healthy ovarian tissue (*Hachisuga and Kawarabayashi, 2002*; *Muzii et al., 2002*), vascular injury during electrocoagulation and autoimmune reactions caused by severe local inflammation (*Garcia-Velasco and Somigliana, 2009*).

Considering the relationship between endometriosis and ovarian reserve, women with endometriosis are potential candidates for fertility preservation. The reduction in the ovarian reserve after surgery is unpredictable and cannot be restored. Moreover, endometriosis is a chronic disorder that tends to recur (*Guo, 2009*; *Vercellini et al., 2013*).

Elizur et al. (2009) published the first case report describing the cryopreservation of 21 oocytes after three cycles of ovarian stimulation in a patient with endometriosis. Following this case report, *Garcia-Velasco et al. (2013)* reported 5 years' experience with oocyte vitrification, which included the results of fertility preservation in 38 patients with endometriosis. They did not, however, describe endometriosis in detail, e.g. cyst size or laterality. *Cobo et al. (2016)* described survival and live birth rate of electively vitrified oocytes after assessing 12 patients with endometriosis. Clinical data on oocyte cryopreservation on women with endometriosis, however, are limited.

No study has analysed detailed information on endometrioma in patients who cryopreserved oocytes through ovarian stimulation before surgery. Hence, the aim of the present study was to evaluate the clinical characteristics and cycle outcomes of oocyte cryopreservation for fertility preservation in women with ovarian endometriosis before ovarian cystectomy.

MATERIALS AND METHODS

Study design

This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital on 15 July 2019 (B-1808/487-103). A total of 34 women who underwent oocyte cryopreservation for fertility preservation between May 2016 and May 2019 were recruited retrospectively from the tertiary university medical centre. Inclusion criteria were as follows: women diagnosed with ovarian endometriosis on imaging; women for whom ovarian cystectomy was planned owing to the severity of symptoms or increasing size of the endometrioma; and women who underwent oocyte cryopreservation before ovarian surgery for fertility preservation.

The primary objective of this study was to present fertility preservation outcomes in patients with endometrioma, such as the number of oocytes cryopreserved, the number of oocytes retrieved and the total dose of gonadotrophin. First, the clinical characteristics and ovarian stimulation outcomes of women with endometrioma undergoing fertility preservation were described and the results were sub-analysed according to laterality. In addition, the change of endometrioma after ovarian stimulation and surgical findings were analysed. Second, the first ovarian stimulation cycle outcomes were compared between women with endometrioma undergoing fertility preservation and women with infertility without endometrioma in a propensity score-matched cohort. Infertile patients caused by male factors, tubal factors or unexplained causes, who had undergone IVF treatment with ovarian stimulation during the same period, were enrolled. The propensity scores were calculated using logistic regression analyses based on the following patients' baseline variables: age and body mass index (BMI). One woman who had undergone fertility preservation was matched to one woman treated with IVF using a propensity score (Supplementary Figure 1). Third, the number of oocytes cryopreserved in repeated ovarian stimulation cycles were analysed and the differences between the cycles were evaluated.

Procedures

Women with endometrioma who were scheduled to undergo ovarian cystectomy were counselled about fertility preservation. Serum AMH (Elecsys assay, Roche Diagnostics, Switzerland) was measured to assess the ovarian reserve before ovarian stimulation. Oocyte cryopreservation was recommended when the ovarian reserve was not high enough (when AMH was lower than the expected value for age, or less than 3.0 ng/ml), in cases of bilateral endometrioma or recurrent endometrioma, or if the patient requested it. If the number of oocytes retrieved for cryopreservation was insufficient in the first round, ovarian stimulation was repeated to accumulate more oocytes. The goal was to cryopreserve around 10 oocytes.

The diagnosis of endometriosis was made when a typical endometrioma was seen on ultrasound examination. Postoperatively, the lesion was confirmed histologically. A typical endometrioma was diagnosed if an ovarian cyst with regular margins and ground glass echogenicity was shown on ultrasound examination (*Exacoustos et al., 2014*).

All the women underwent ovarian cystectomy under general anaesthesia. Full inspection of the pelvis was undertaken, and surgical findings were scored according to the Revised American Society for Reproductive Medicine classification (*American Society for Reproductive Medicine, 1997*). Successful removal of a cyst consisted of removing the endometrioma contents as well as the cyst wall. Hemostasis was achieved by carefully applying the bipolar forceps on the ovarian parenchyma if necessary. The ovarian capsule was sutured with absorbable suture thread. Adhesions present in the ovary and the uterus were dissected. The patients were kept under observation in the inpatient room for 2 days after the operation. One week after the surgery, the patients were admitted to the outpatient clinic and prescribed medication for the prevention of recurrence; dienogest (Visanne, 2 mg) (Bayer, Berlin, Germany) was mainly used.

Ovarian stimulation and vitrification of oocytes

All patients underwent ovarian stimulation with pituitary suppression by gonadotrophin-releasing hormone (GnRH) antagonist. Determination of the initial dose of recombinant FSH (Gonal-F) (Serono, Geneva, Switzerland) was based on age and serum AMH level. If the leading follicle attained a mean diameter of 14 mm, GnRH antagonist (Cetrorelix 0.25 mg) (Serono, Darmstadt, Germany) was given for prevention of premature ovulation. When the diameter of the largest follicle reached 18 mm, recombinant HCG (Ovidrel, 250 μg) (Serono, Darmstadt, Germany) was provided to mature the oocytes. The oocytes were retrieved under transvaginal ultrasound guidance 36 h after HCG triggering. The ovarian stimulation method was the same as that conducted in patients with infertility.

The oocyte maturity was evaluated and confirmed by at least two experts under microscopic examination. The three stages in oocyte development are mature (metaphase II), intermature (metaphase I), and immature. Mature oocytes and in vitro-matured oocytes were cryopreserved by the vitrification method.

Statistical analyses

SPSS 22.0 (IBM Corp., USA) was used for statistical analyses. Data were compared by Student's t-test, and Pearson's chi-squared test and Fisher's exact test were used for comparison of independent variables. Propensity score, calculated by age and BMI, was used for matching. For repeated cycle data, generalized estimating equation was used for comparison of ovarian stimulation outcomes according to laterality and Wilcoxon signed rank test for comparing the first and second cycle outcomes. Descriptive data are expressed as median with range or mean ± SD for continuous data and as proportions for categorical data. $P < 0.05$ was considered statistically significant.

RESULTS

During the study period, ovarian cystectomy for endometrioma were planned for 141 patients. Of these, 19 patients were not willing to have a child after surgery, so the fertility preservation procedure was not recommended to these patients. After measuring serum AMH in patients, 68 were advised to consider fertility preservation. Finally, three patients (4.4%) chose embryo cryopreservation, 34 (50.0%) underwent oocyte cryopreservation and 31 (45.6%) refused to undergo fertility preservation.

A total of 34 women with ovarian endometriosis underwent ovarian stimulation for oocyte cryopreservation. All the enrolled patients were unmarried. The clinical characteristics of the patients according to the laterality are presented in TABLE 1. The mean age, BMI, basal FSH and serum AMH levels were 30.7 ± 5.9 years, 21.1 ± 2.5 kg/m^2, 6.4 ± 2.9 mIU/ml, and 1.85 ± 1.14 ng/ml, respectively. The mean diameter of the largest endometrioma at the time of diagnosis was 6.0 ± 2.5 cm. Multiple endometriotic cysts were present in 17.6% of patients. All clinical characteristics were similar between patients with bilateral endometrioma and those with unilateral endometrioma. No patient undergoing fertility preservation had deep infiltrating endometriosis. The mean score of Revised American Society for Reproductive Medicine among the study participants was 60 ± 36. Ovarian stimulation outcomes in the patients from 50 cycles according to the laterality are

TABLE 1 CLINICAL CHARACTERISTICS OF PATIENTS WITH ENDOMETRIOMA ACCORDING TO LATERALITY

Variables	Total (n = 34)	Unilateral endometrioma (n = 16)	Bilateral endometrioma (n = 18)	P-value
Age, years	30.7 ± 5.9	30.9 ± 6.1	30.6 ± 5.8	0.877
BMI, kg/m^2	21.1 ± 2.5	20.8 ± 2.2	21.3 ± 2.8	0.544
Basal FSH, mIU/ml	6.4 ± 2.9	7.1 ± 2.7	5.8 ± 3.1	0.235
AMH, ng/ml	1.85 ± 1.14	1.72 ± 1.12	1.96 ± 1.18	0.547
Previous ovarian surgery before ovarian stimulation, n (%)	11 (32.4)	5 (31.3)	6 (33.3)	0.897
Diameter of largest cyst at Diagnosis, cm	6.0 ± 2.5	5.3 ± 2.2	6.6 ± 2.6	0.126
Number of cysts, n (%)				0.660
Single	28 (82.4)	14 (87.5)	14 (77.8)	
Multiple	6 (17.6%)	2 (12.5)	4 (22.2)	

Data are presented as number (%), or mean ± SD.

AMH, anti-Müllerian hormone; BMI, body mass index.

TABLE 2 OUTCOMES OF OVARIAN STIMULATION CYCLES ACCORDING TO ENDOMETRIOMA LATERALITY

Variables	Total (n = 50)	Unilateral endometrioma (n = 22)	Bilateral endometrioma (n = 28)	P-value
Number of patients participating in the stimulation cycle				
First cycle	34	16	18	
Second cycle	13	5	8	
Third cycle	3	1	2	
Total dose of gonadotrophins, IU	2468 ± 507	2594 ± 568	2368 ± 438	<0.001
Duration of stimulation, day	8.4 ± 1.5	8.7 ± 1.8	8.2 ± 1.2	<0.001
Peak serum oestradiol levels, pg/ml	1331 ± 1,131	1752 ± 1,312	984 ± 846	0.291
Number of oocytes retrieved, n	6.3 ± 4.3	7.2 ± 4.6	5.5 ± 3.9	0.651
Number of mature oocytes retrieved, n	4.1 ± 3.1	5.1 ± 3.6	3.3 ± 2.4	0.065
Percentage of mature oocytes, % (n)	65.8 (206/313)	71.5 (113/158)	60.0 (93/155)	0.032
Number of oocytes cryopreserved, n	4.8 ± 3.2	5.7 ± 3.4	4.1 ± 2.9	0.600
Percentage of cryopreserved oocytes, % (n)	77.3 (242/313)	79.7 (126/158)	74.8 (116/155)	0.300

Data are presented as mean ± SD, number, or % (number).

presented in TABLE 2. Thirteen patients (38.2%) underwent ovarian stimulation more than once. The total dose of gonadotrophins, duration of stimulation, and peak oestradiol levels were 2468 ± 507 IU, 8.4 ± 1.5 days, and 1331 ± 1131 pg/ml, respectively. The mean number of oocytes retrieved was 6.3 ± 4.3, the mean number of mature oocytes retrieved was 4.1 ± 3.1, and the mean number of oocytes cryopreserved was 4.8 ± 3.2. The percentage of mature oocytes and the percentage of cryopreserved oocytes were 65.8% and 77.3%, respectively. The average duration from the start of the first ovarian stimulation cycles to the day of surgery was 65.5 ± 64.9 days.

Subgroup analysis was conducted according to laterality of endometriomas. Overall, 18 women with bilateral endometrioma underwent 28 ovarian stimulation cycles, and 16 women with unilateral endometrioma underwent 22 ovarian stimulation cycles. No difference was observed between patients with bilateral and unilateral endometriomas in AMH levels (1.72 ± 1.12 versus 1.96 ± 1.18 ng/ml; $P = 0.547$) (TABLE 1). The total dose of gonadotrophins and duration of stimulation were lower in patients with bilateral endometrioma than in those with unilateral endometrioma (2368 ± 438 versus 2594 ± 568 IU, $P < 0.001$; and 8.2 ± 1.2 versus 8.7 ± 1.8 days, $P < 0.001$). The peak serum oestradiol and the number of oocytes retrieved in patients with bilateral endometrioma compared with those in patients with unilateral endometrioma were 984 ± 846 versus 1752 ± 1312 pg/ml, $P = 0.291$; and 5.5 ± 3.9 versus 7.2 ± 4.6, $P = 0.651$, respectively. The percentage of mature oocytes was significantly lower in patients with bilateral endometrioma than in those with unilateral endometrioma (60.0% versus 71.5%; $P = 0.032$). The number of oocytes cryopreserved in bilateral endometrioma group compared with unilateral endometrioma was 4.1 ± 2.9 versus 5.7 ± 3.4 ($P = 0.600$). In patients with unilateral endometrioma, the number of oocytes retrieved from the affected ovary was 2.9 ± 2.7 compared with 3.9 ±3.4 retrieved from the contralateral ovary ($P = 0.359$). The mean diameter of the largest cyst measured by ultrasound the day before surgery was 6.0 ± 2.7 cm. The endometrioma size did not differ before and after ovarian stimulation.

TABLE 3 COMPARISON OF CLINICAL CHARACTERISTICS AND FIRST OVARIAN STIMULATION CYCLE OUTCOMES OF PATIENTS WITH ENDOMETRIOMA UNDERGOING FERTILITY PRESERVATION AND PATIENTS WITH INFERTILITY WITHOUT ENDOMETRIOMA AFTER PROPENSITY SCORE MATCHED

Variables	Patients with endometrioma undergoing fertility preservation (n = 22)	Infertile patients without endometrioma (n = 22)	P-value
Age, years	33.3 ± 4.9	33.3 ± 4.3	1.000
BMI, kg/m^2	21.0 ± 2.1	21.2 ± 2.0	0.752
Basal FSH, mIU/ml	6.3 ± 2.8	5.4 ± 2.6	0.528
AMH, ng/ml	1.98 ± 1.29	2.77 ± 0.91	0.032
Total dose of gonadotrophins, IU	2345 ± 439	1838 ± 624	0.003
Duration of stimulation, day	8.0 ± 1.3	7.3 ± 1.5	0.106
Peak serum oestradiol levels, pg/ml	1385 ± 1,164	1734 ± 1009	0.913
Number of oocytes retrieved, n	5.4 ± 3.8	8.1 ± 4.8	0.045
Number of mature oocytes retrieved, n	3.8 ± 3.0	4.7 ± 3.7	0.402

Data are presented as mean ± SD.

AMH, anti-Müllerian hormone; BMI, body mass index.

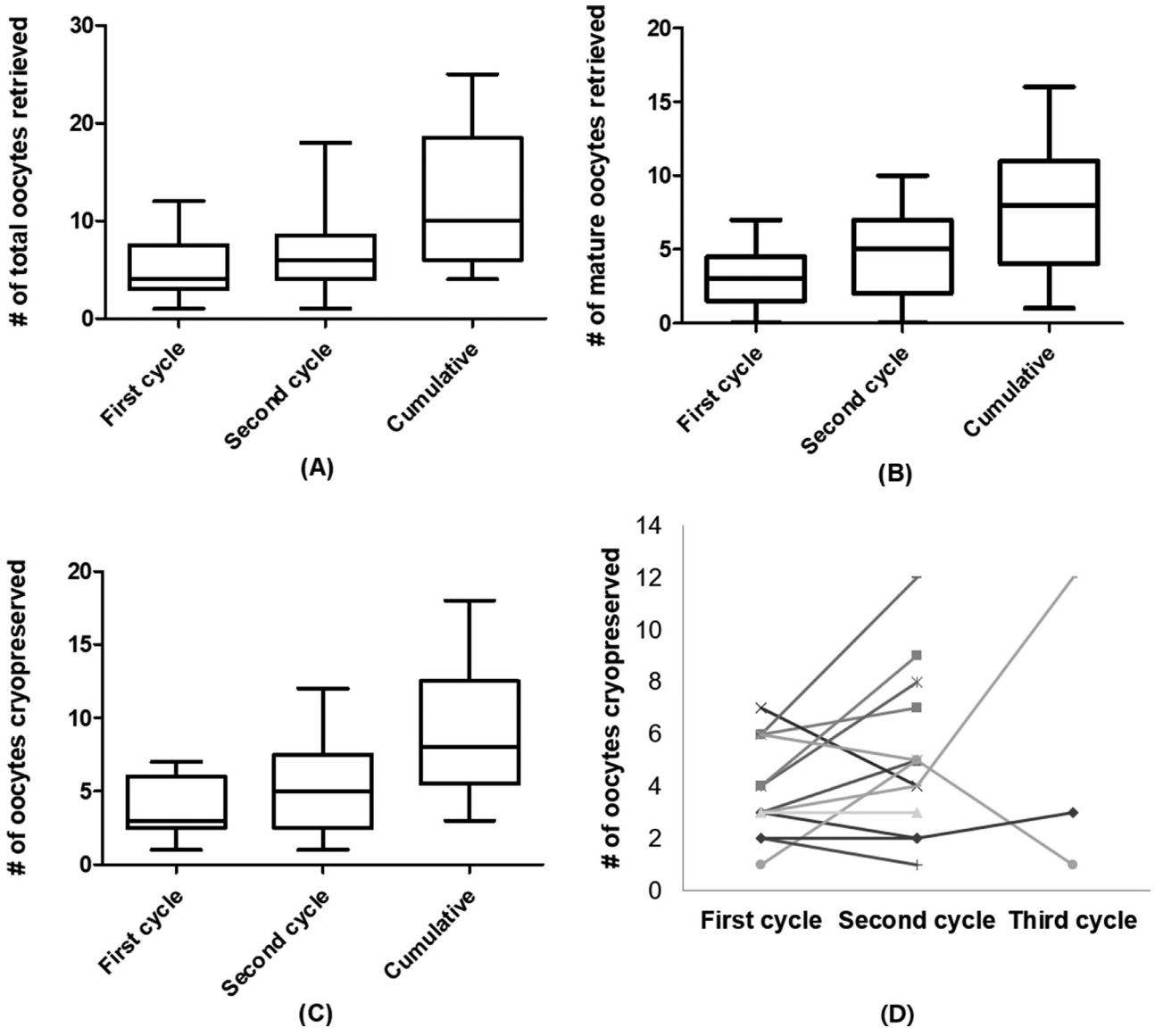

FIGURE 1 (A) Cumulative total number of oocytes retrieved; (B) number of mature oocytes retrieved; and (C) number of oocytes cryopreserved from the first and second stimulation cycles in 13 patients with ovarian endometriosis who underwent at least two ovarian stimulation cycles. Data are shown as box and whisker plots. The lines inside boxes represent the medians, and the upper and lower bounds of boxes and whiskers represent interquartile and full ranges; (D) individual data for the number of oocytes cryopreserved in the first, second and third cycles.

The clinical characteristics and ovarian stimulation outcomes of the first cycle in patients with endometrioma undergoing fertility preservation and patients with infertility without endometrioma are presented in TABLE 3. Although age and BMI were similar, patients undergoing fertility preservation with endometrioma had lower AMH levels and received a higher total dose of gonadotrophins compared with those of infertile patients without endometrioma (1.98 ± 1.29 versus 2.77 ± 0.91 ng/ml, $P = 0.032$; 2345 ± 439 versus 1838 ± 624 IU, $P = 0.003$, respectively). The duration of stimulation and the peak serum oestradiol levels in patients with endometrioma undergoing fertility preservation and those in infertile patients without endometrioma were 8.0 ± 1.3 versus 7.3 ± 1.5 days and 1385 ± 1164 versus 1734 ± 1009 pg/ml, respectively. The number of oocytes retrieved was significantly lower in patients with endometrioma undergoing fertility preservation (5.4 ± 3.8 versus 8.1 ± 4.8, $P = 0.045$), but the number of mature oocytes retrieved was not statistically different (3.8 ± 3.0 versus 4.7 ± 3.7, $P = 0.402$).

The number of oocytes cryopreserved in repeated stimulation cycles in patients with ovarian endometriosis ($n = 13$) are presented in FIGURE 1. Cryopreserved oocyte number (median [interquartile range]) at the first, second, and the third cycle were 3.0 [2.5, 6.0], 5.0 [2.5, 7.5], and 3.0 [2.0, 7.5], respectively. No difference was found in the number of oocytes cryopreserved in the first cycle and the second cycle ($P = 0.127$).

DISCUSSION

In this study, we report on the feasibility of ovarian simulation and oocyte cryopreservation for women undergoing fertility preservation with endometriomas. Patients with endometrioma undergoing fertility preservation had a lower ovarian reserve than women of the same age

without endometrioma. Fewer oocytes were retrieved from patients with endometrioma undergoing fertility preservation. Nevertheless, repeated ovarian stimulation can increase the number of oocytes for cryopreservation. Repeated oocyte retrieval in women with endometrioma did not affect the number of oocytes retrieved per cycle.

In the present study, patients with bilateral endometrioma had a lower percentage of mature oocytes than those with unilateral endometrioma, despite the similarity of serum AMH levels in the two groups. The number of oocytes cryopreserved, number of oocytes retrieved, number of mature oocytes retrieved and percentage of cryopreserved oocytes seemed to be lower in patients with bilateral endometrioma than in patients with unilateral endometrioma, although no statistically significant differences could be found, which was possibly because of the small size of the study population. Our results are consistent with those of a previous study that reported decreased ovulation in the affected ovary compared with the normal ovary (*Horikawa et al., 2008*). Furthermore, the postoperative serum AMH level decreases more in bilateral endometrioma than in unilateral endometrioma patients (*Chang et al., 2010*). Therefore, our study suggests that, in cases of bilateral endometrioma, fertility preservation should be carried out even when the AMH level is relatively high.

We arbitrarily set a serum AMH level threshold of 3.0 ng/ml when recommending oocyte cryopreservation before ovarian cystectomy. According to one study, the serum AMH level decreased from 3.0 ng/ml (range 0.5–12.1 ng/ml) to 2.2 ng/ml (range 0.1–7.2 ng/ml) after endometrioma surgery (*Iwase et al., 2010*). The reduction in the ovarian reserve after surgery is unpredictable in each patient. Further study is necessary to set a proper cut-off level.

As the baseline ovarian reserve is often reduced in endometrioma patients, one ovarian stimulation may not be able to secure a sufficient number of oocytes as required for cryopreservation. In such cases, repetitive ovarian simulation cycles can increase the number of oocytes available for cryopreservation. Although a third cycle was only carried out in three patients, the results indicate that repeated ovarian stimulation and oocyte cryopreservation were feasible. As the number of oocytes cryopreserved in the second cycle is similar to that cryopreserved from the first cycle, it was possible to cryopreserve about twice as many oocytes in total. Repeated ovarian stimulation in women with endometrioma did not affect the number of oocytes cryopreserved. Moreover, because surgery for endometriomas is not urgent, it is possible to postpone the surgery and carry out ovarian stimulation again.

More oocytes are required for live birth as female age increases (*Doyle et al., 2016*). It is impossible to obtain an optimal number of oocytes guaranteeing at least one live birth in every woman. We also considered that, unlike fertility preservation in cancer patients, in endometriosis patients, more oocytes can be cryopreserved even after surgery if necessary. Therefore, we set a minimum of 10 oocytes for fertility preservation in women with endometrioma before surgery. Further study on the optimal cut-off number of oocytes is needed.

Kasapoglu et al. (2018) recently reported the rate of decline of ovarian reserve in patients with endometrioma who were not treated (*Kasapoglu et al., 2018*). This prospective study of 6 months' follow-up showed more rapid AMH level decrease in patients with endometrioma who were not treated than that in age-matched healthy controls. Therefore, if endometrioma is present, active treatment, including surgical treatment should be considered. Because of the detrimental effect of ovarian cystectomy on ovarian reserve (*Chang et al., 2010*; *Raffi et al., 2012*; *Somigliana et al., 2012*), however, women with ovarian endometriosis should consider oocyte cryopreservation for fertility preservation before undergoing surgery. No consensus has been reached on the strategy for fertility preservation in women with endometriosis, but professionals argue against the introduction of fertility preservation for endometriosis in routine clinical practice based on the lack of clinical data (*Somigliana et al., 2015*; *Streuli et al., 2018*). Further research on fertility preservation in women with endometriosis should be conducted.

Although pelvic inflammatory disease rarely occurs after oocyte retrieval, the presence of endometriosis is a risk factor for pelvic inflammatory disease (*Romero et al., 2013*). The development of pelvic abscess after oocyte retrieval in patients with endometriosis is rare and has been reported in case reports (*Benaglia et al., 2008*). The effectiveness of antibiotic prophylaxis and the best antibiotic to use are controversial (*Romero et al., 2013*). In the present study, antibiotic prophylaxis was provided for all the patients who underwent oocyte retrieval, and no adverse events of infection after the procedure occurred. If a follicle was behind an endometrioma, we penetrated the endometrioma and extracted the oocyte. Nevertheless, no additional complications associated with endometrioma rupture occurred. Furthermore, women with endometrioma are usually concerned about the risk of progression of the endometriosis during the time taken for ovarian stimulation. Our study, however, showed no increase in the size of endometrioma after ovarian stimulation. Considering the short duration of ovarian stimulation and surgery immediately after ovarian stimulation, the possibility of disease progression seems to be low.

The effect of endometriosis on oocyte quality is controversial. From a systematic review of the literature (*Sanchez et al., 2017*), it has been shown that women with endometriosis had oocytes with lower in-vitro maturation rate, more altered morphology and lower cytoplasmic mitochondrial content compared with infertile women with other causes. The embryo aneuploidy rate was similar in patients with endometriosis who underwent IVF and unaffected age-matched controls (*Juneau et al., 2017*). The fertilization rate of oocytes collected from patients with endometriosis was lower than that in the controls (*Barnhart et al., 2002*; *Harb et al., 2013*). In situations in which the quality of the oocytes is not optimal, it would be beneficial to increase the number of oocytes collected or reduce the activity of the endometriosis by pretreatment. Further study is necessary to elucidate these issues.

The debate about the best ovarian stimulation protocol for a patient with endometriosis is ongoing. The European Society of Human Reproduction and Embryology guidelines suggest that ultra-long GnRH agonist treatment can be considered in women with endometriosis to improve clinical

pregnancy rate (*Dunselman et al., 2014*). This recommendation, however, is based on one meta-analysis published in 2006 (*Sallam et al., 2006*). In this meta-analysis, only three randomized clinical trials were included, and the investigators could not conclude whether the improvement in the pregnancy rate was a result of better oocytes or better endometrial receptivity. Therefore, evidence that GnRH agonist long or ultra-long treatment is better for oocyte quality by suppressing endometrioma is lacking. In fertility preservation, because the number of oocytes is the main concern, not the pregnancy rate after fresh embryo transfer, the GnRH antagonist protocol is applicable as shown in our study.

The present study has a few limitations, such as the retrospective study design and the small number of study participants. Moreover, only the result of oocyte cryopreservation was reported, and results after warming were not presented.

In conclusion, as ovarian endometriosis requires active treatment and ovarian cystectomy tends to decrease the ovarian reserve, women with ovarian endometriosis should be counselled about oocyte cryopreservation for fertility preservation before surgery. Repeated oocyte retrieval would help obtain more oocytes for preserving future fertility.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2020.01.028.

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