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Analyzing the risk factors for a diminished oocyte retrieval rate under controlled ovarian stimulation

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Abstract

Aim: To investigate which risk factors contribute to a lower oocyte retrieval ratio in women who are receiving controlled ovarian hyperstimulation.

Methods: The authors retrospectively analyzed 329 in vitro fertilization (IVF) cycles under controlled ovarian hyperstimulation by using a gonadotropin-releasing hormone antagonist or agonist at Osaka Medical College, Japan. The patients were classified into five groups: advanced age, male infertility, severe endometriosis, tubal infertility, and unexplained infertility. The primary outcomes were the patients' age, oocyte retrieval ratio, serum basal follicle-stimulating hormone, total dose of gonadotropin, and the clinical outcome. A secondary outcome was the stepwise multivariate logistic regression analysis to assess the factors associated with the failure of oocyte retrieval.

Results: The oocyte retrieval ratio declined significantly with the patient's age. The ratio of endometriosis in unsuccessful cases was significantly higher than that in successful cycles. Advanced age and endometriosis were the factors that were significantly associated with a lowered oocyte retrieval rate.

Conclusion: Advanced age and endometriosis are high-risk factors that contribute to oocyte retrieval failure in infertile patients who are receiving IVF treatment.

KEYWORDS

advanced age, controlled ovarian hyperstimulation, endometriosis, oocyte retrieval ratio, unexplained infertility

1 | INTRODUCTION

The tendency to marry later is becoming a major cause of infertility in Japan. Assisted reproductive technology (ART) is widely used in infertility treatment; however, deciding on an appropriate regimen for poor-responder patients who are preparing for assisted reproductive techniques is quite difficult.[1] The success of in vitro fertilization (IVF) largely depends on the number and quality of retrieved oocytes following controlled ovarian hyperstimulation (COH). A variety of protocols has been reported with varying degrees of success, ranging from the unstimulated cycle to COH using clomiphene, urinary and recombinant gonadotropins, adjunctive gonadotropin-releasing hormone (GnRH) agonists and antagonists, bromocriptine, growth hormone, and growth hormone-releasing hormone. Factors, such as the basal antral follicle count with scanning and an elevated basal serum follicle-stimulating hormone (FSH) level greater than 15 IU/mL in the early follicular phase, have been used to define a "poor response" to ovarian stimulation.[1,2] On the other hand, we have encountered cases in which no oocyte was recovered, regardless of the development of multiple mature follicles. Regardless, obtaining a scant number of oocytes from numerous mature follicles that have just appeared is a frustrating experience that is more commonly encountered. It remains unclear, however, which

factors most affect the oocyte retrieval rate, thus defined as the number of retrieved oocytes/aspirated follicles × 100. The primary aim of this study was to assess which predictive factors contribute to a lower oocyte retrieval rate and which provide an accurate estimation of the number of retrieved oocytes in patients undertaking ART under COH.

2 | MATERIALS AND METHODS

Three-hundred-and-twenty-nine patients who underwent COH under a GnRH agonist (short protocol) or GnRH antagonist for IVF between 2008 and 2012 at Osaka Medical College, Japan, were enrolled in this study. This was a retrospective cross-sectional, case-controlled study of the oocyte retrieval ratio in IVF or intracytoplasmic sperm injection cycles. The inclusion criteria for patients were as follows: (1) 34–47 years of age with regular menstrual cycles; (2) the absence of endocrine disease; and (3) the diagnosis of endometriotic cysts by transvaginal ultrasound and by magnetic resonance imaging, followed by laparoscopic surgery. The exclusion criteria for patients were as follows: (1) a FSH level suggestive of menopause; (2) the suspicion of malignant ovarian disease; and (3) oral contraceptive use within 3 months before surgery. No patient had taken preoperative hormonal treatment. The infertile patients were classified into five groups: advanced age (older than 35 years old), severe endometriosis, male infertility, tubal infertility, and unexplained infertility (Table 1). All the patients with severe endometriosis and tubal infertility undertook a laparoscopic bilateral endometriotic cystectomy for endometriotic cysts and a subsequent salpingectomy for ectopic pregnancy within 1 year of oocyte retrieval respectively. Unexplained infertility was confirmed following a standard infertility evaluation, including a semen analysis, assessment of ovulation, hysterosalpingogram, and hysteroscopy. Our Institutional Review Board approved this protocol (No. 66) and its consent form and informed consent was obtained from all the participants.

Under the GnRH antagonist protocol, the women who enrolled started IVF cycles using the GnRH antagonist and, on day 3 of the treatment cycle, controlled ovarian stimulation was started by the daily injection of human menopausal gonadotropin (hMG) (HMG Teizo, Tokyo, Japan) at a dose of 150–300 IU/d. A daily dose of 0.25 mg of a GnRH antagonist (Cetrotide) was initiated when the mean diameter of the leading follicle had reached 14–15 mm on transvaginal ultrasound.

TABLE 1 Patients characteristic

Variables	Values
Median age (years)	37.8 (34–47)
Serum basal FSH level (mIU/mL)	10.5 (0.6–30.2)
Major cause of infertility (%)	
Advanced age	224 (50.2)
Endometriosis	73 (22.2)
Male infertility	130 (39.5)
Tubal infertility	42 (12.8)
Unexplained	16 (4.9)

FSH, follicle-stimulating hormone.

Under the short protocol, 600 μg of GnRH agonist (Suprecur, Mochida, Tokyo, Japan) was started on day 1 and controlled ovarian stimulation was started by the daily injection of hMG (HMG Teizo, Asuka, Tokyo, Japan) at a dose of 150 IU/d up to 300 IU on day 3. In both protocols, 10 000 IU of human chorionic gonadotropin (Gonadotropin, Asuka, Tokyo, Japan) was administered intramuscularly when the leading follicles reached a diameter of greater than 18 mm and transvaginal oocyte retrieval was performed 35 hours later. The oocyte retrieval ratio (%) was calculated as follows: the total number of retrieved oocytes/the total number of basal antral follicles × 100. Hormone assays, follicle monitoring, oocyte retrieval, insemination, embryo culture, embryo transfers, and the confirmation of embryo quality were performed as previously reported.[3] Hormone assaying was performed at the time of oocyte retrieval and the basic values for luteinizing hormone and FSH were assayed at the time of the basal antral follicle count. The number of basal antral follicles was counted at day 2 before starting hMG/FSH administration. Pregnancy was confirmed by the identification of an intrauterine gestational sac during an ultrasound examination.

2.1 | Statistical analysis

The statistical analysis was conducted with StatMate IV (ATMS Co., Ltd., Tokyo, Japan). Comparisons between the two non-parametric groups were performed with the non-parametric Mann-Whitney *U* test, the parametric unpaired *t* test, or the chi-square test. The Pearson's correlation coefficient was performed for the normally distributed data and differences were considered to be statistically significant at $P<.05$. A stepwise multivariate regression analysis was performed in order to investigate the independent variables associated with a decline in the oocyte retrieval rate. All the parameters that significantly correlated with a decline in the oocyte retrieval rate were subsequently evaluated in the forward stepwise multivariate regression model.

A stepwise multivariate logistic regression analysis also was performed in order to assess the factors that were associated with a decline in the oocyte retrieval rate. A *P*-value of <.05 was considered as statistically significant.

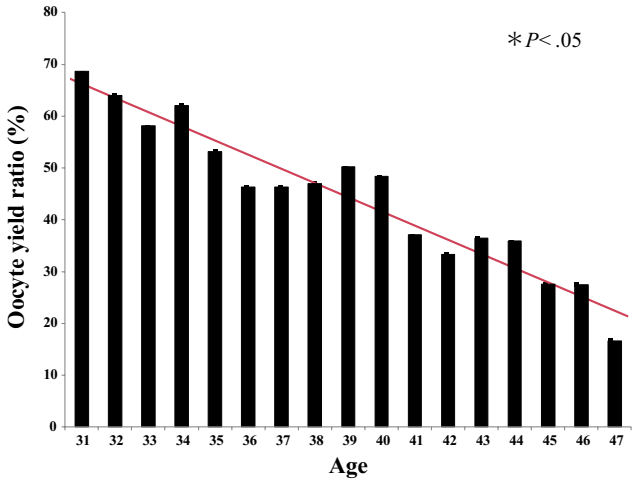

FIGURE 1 Relationship between the oocyte retrieval ratio and the patient's age

3 | RESULTS

The median age of the study group as a whole was 37.8 years (range 34-47 years). The median serum basal FSH level was 10.5 mIU/mL (range 0.6-30.2 mIU/mL). Advanced age was the most frequently identified cause of infertility (Table 1); moreover, the oocyte retrieval ratio correlated negatively with age (Figure 1).

The mean age, serum basal FSH level, and total dose of hMG were significantly higher in the unsuccessfully retrieved cycles (URCs; a cycle in which no oocyte was retrieved) than in the successfully retrieved cycles (SRCs; a cycle in which more than one oocyte was retrieved) ($P<.05$). The number of aspirated follicles in the URCs was significantly lower than that in the SRCs. As well, the ratio of women associated with severe endometriosis was significantly higher in the URCs than in the SRCs (Table 2). Table 3 reveals the clinical outcomes according to each infertility factor. The age and basal serum FSH level in cases of unexplained infertility were lower than for the other causes of infertility ($P<.05$). The implantation rate in the advanced-age patients and the pregnancy rate in the patients with severe endometriosis were lower than in relation to the other causes of infertility (Table 3). The oocyte retrieval ratio (%) in cases where at least one high-quality embryo was retrieved was statistically higher than that in cases where a high-quality embryo was not available (Figure 2). The univariate and multivariate logistic regressions showed that the oocyte retrieval rate was significantly associated with age and the presence of severe endometriosis (Figure 3).

TABLE 2 Patients characteristic

Variables	Successfully Retrieved n=258	Unsuccessfully Retrieved n=71	*P*
Age (years)	37.9±5.7	39.5±3.9	<.05
No. of antral follicle counts	10.0±6.8	2.5±1.8	<.05
Serum basal FSH level (mIU/mL)	9.5±7.0	14.9±12.0	<.05
Total dose of hMG/FSH (IU)	3190.4±1546.0	3572.9±2409.4	>.05
Advanced age (%)	67.4	100.0	>.05
Endometriosis (%)	19.8	31.0	>.05
Male infertility (%)	37.6	22.5	>.05
Tubal infertility (%)	14.7	5.6	>.05
Unexplained infertility (%)	5.0	4.2	>.05

FSH, follicle-stimulating hormone; hMG, human menopausal gonadotropin. Values are presented as the mean±SD or %. Comparisons between the two non-parametric groups were performed with the non-parametric Mann-Whitney *U* test or the parametric unpaired *t* test or chi-square test.

4 | DISCUSSION

In many IVF cycles, in spite of the numerous developed follicles that are visualized at the time of ultrasound, a scant number of oocytes is often retrieved and thus leads to a poor pregnancy outcome. This study revealed that the oocyte retrieval rate declines significantly with age. There is an evident gradual decline in female fecundity with age, particularly noticeable in those who are older than 30 years, accelerating between the ages of 35 and 40, and reducing to almost zero by 45 years.[4,5] There is also a decrease in the ovarian reserve with age, caused by the decreased number of oocytes and the concomitant increase in the rate of oocyte aneuploidy and subsequent reduced reproductive potential.[6] It was reported that women who were older than 40 years and who had not been pregnant with their own oocytes showed a significantly higher pregnancy rate by using donated oocytes from young women.[7] These data support the idea

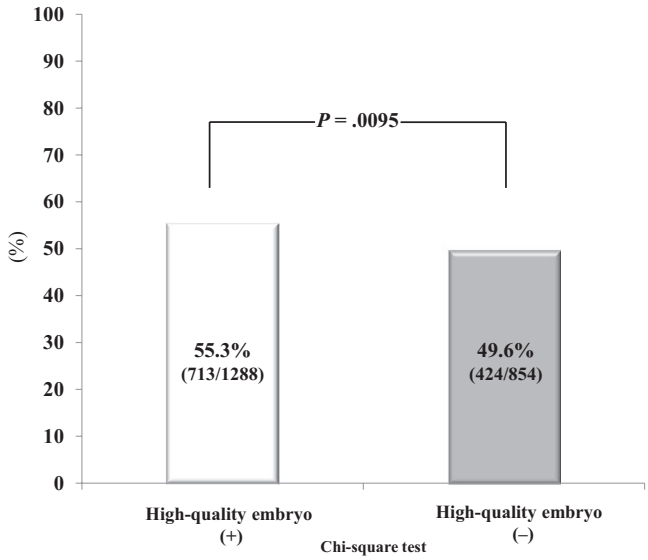

FIGURE 2 The oocyte retrieval ratio (%) in cases where at least one high-quality embryo was retrieved was statistically higher than that in cases where a high-quality embryo was not available

TABLE 3 The clinical outcomes according to each infertility factor

Variables	Age Factor n=224	Endometriosis n=73	Male Factor n=130	Tubal Factor n=42	Unexplained n=16
Age (years)	39.6±3.4	36.1±4.2	38.5±4.2	36.4±4.8	31.9±1.9
Serum FSH level at day 3 (IU/mL)	10.8±8.0	10.8±8.2	10.6±7.4	6.9±3.4	5.9±2.5
Oocyte retrieval ratio (%)	46.7	45.2	47.4	48.5	59.3
Pregnancy rate (%)	8.9	8.2	10.8	19.0	56.2

FSH, follicle-stimulating hormone.

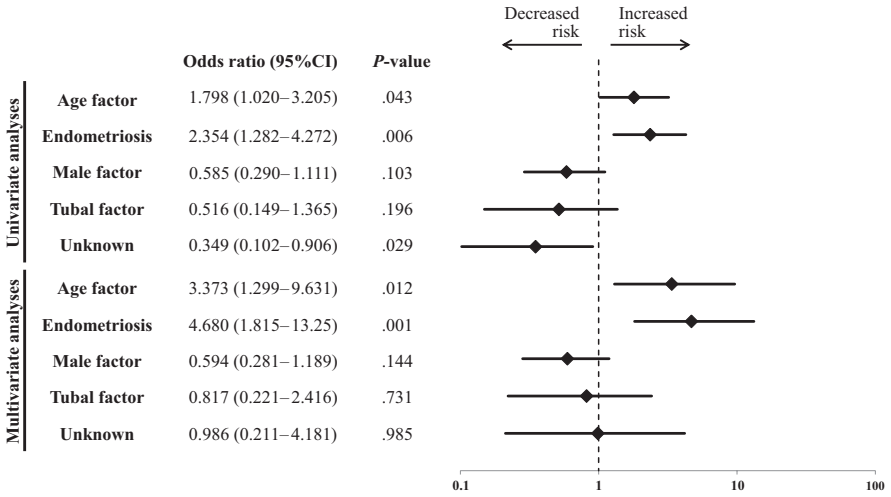

FIGURE 3 Forest plot (univariate/multivariate logistic regression) indicating the association between the cause of infertility and the risk of oocyte retrieval failure among 329 treatment cycles. CI, confidence interval

that a decline in female fecundity with age is largely attributed to oocyte quality.

Endometriosis is still one of the most enigmatic of all gynecological diseases; however, recent epigenetic changes in the disease have gradually come under close investigation.[8,9] Some studies suggest that infertility as a result of endometriosis is caused mainly by an impaired ovarian reserve and reduced ovarian response, as indicated by lower anti-Müllerian hormone, higher FSH, and the aberrant expression of some proteins.[10,11] Several retrospective studies have reported on poor responses to FSH/hMG in patients with endometriosis.[12,13] In particular, the number of retrieved oocytes has been shown to decline in the ovary following a cystectomy for endometriotic cysts.[14] In this study, all the patients with severe endometriosis received a laparoscopic cystectomy and therefore the number of retrieved oocytes was lower in these women than in the patients with other causes of infertility. In order to prevent postoperative ovarian reserve impairment, such as that seen after the treatment of recurrent and bilateral endometriotic cysts, using plasma energy for the ablation of endometrial tissue has been recommended, thus causing minimal damage to the ovarian parenchyma.[15] Recently, it was reported that a combined technique, including the vaporization of cysts in close proximity to the hilus and a cystectomy for distant portions, can preserve the ovarian reserve.[16] Also recently, the potential contribution of inflammation to follicle burnout in cases of endometriotic cysts was reported[17] and the proactive management of endometriotic cysts, including conservative surgery in young women, has been suggested could prevent ovarian dysfunction.[18] Therefore, early detection and treatment should be considered in order to prevent future infertility.

In conclusion, although more studies are necessary, our study indicates that both severe endometriosis and advanced age are the highest risk factors that contribute to a lower oocyte retrieval rate in IVF.

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DISCLOSURES

Conflict of interest: The authors declare no conflict of interest. *Human rights statement and informed consent*: All the procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all the patients to be included in the study. *Animal studies*: This article does not contain any study with animals that was performed by any of the authors.

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