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

Mayumi Nakamura¹ | Yoshiki Yamashita¹,² | Atsushi Hayashi¹ | Natsuho Saito¹ | Masae Yu¹ | Masami Hayashi¹ | Yoshito Terai¹ | Masahide Ohmichi¹

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, 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](image-url)  
*P<.05

| 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.
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).

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

### 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.

### 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.
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. 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. Several retrospective studies have reported on poor responses to FSH/hMG in patients with endometriosis. In particular, the number of retrieved oocytes has been shown to decline in the ovary following a cystectomy for endometriotic cysts. 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. 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. Also recently, the potential contribution of inflammation to follicle burnout in cases of endometriotic cysts was reported and the proactive management of endometriotic cysts, including conservative surgery in young women, has been suggested could prevent ovarian dysfunction. 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.

ACKNOWLEDGEMENTS

The authors thank Ms. K. Sato and Ms. J. Hayashi for technical assistance with the Western-blotting and real-time polymerase chain reaction techniques.

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

DISCLOSURES

Conflict of interest: The authors declare no conflict of interest.

REFERENCES

1. Surrey ES, Schoolcraft WB. Evaluating strategies for improving ovarian response of the poor responder undergoing assisted reproductive techniques. Fertil Steril. 2000;73:667–676.
2. Hellberg D, Waldenström U, Nilsson S. Defining a poor responder in in vitro fertilization. Fertil Steril. 2004;82:488–490.
3. Yamashita Y, Ueda M, Takehara M, Terai Y, Hang YC, Ueki M. Influence of severe endometriosis on gene expression of vascular endothelial growth factor and interleukin-6 in granulosa cells under controlled ovarian stimulation for IVF–ET. Fertil Steril. 2002;78:865–871.
4. Menken J, Russell J, Larsen U. Age and infertility. Science. 1986;233:1389–1394.
5. Baird DT, Collins J, Egozcue J, et al. Hum Reprod Update. 2005;11:261–276.
6. Magarelli PC, Pearlstone AC, Buyalos RP. Discrimination between chronological and ovarian age in infertile women aged 35 years and older: predicting pregnancy using basal follicle stimulating hormone, age and number of ovulation induction/intra-uterine insemination cycles. Hum Reprod. 1996;11:1214–1219.
7. Navot D, Bergh PA, Williams MA, et al. Poor oocyte quality rather than implantation failure as a cause of age-related decline in female fertility. Lancet. 1991;337:1375–1377.
8. Trukhacheva E, Lin Z, Reierstad S, Cheng YH, Milad M, Bulun SE. Estrogen receptor (ER) beta regulates ERalpha expression in stromal cells derived from ovarian endometriosis. J Clin Endocrinol Metab. 2009;94:615–622.
9. Bulun SE. Endometriosis. N Engl J Med. 2009;360:268–279.
10. Yoo JH, Cha SH, Park CW, et al. Serum anti-Müllerian hormone is a better predictor of ovarian response than FSH and age in IVF patients with endometriosis. Clin Exp Reprod Med. 2011;38:222–227.
11. Prieto L, Quesada JF, Cambero O, et al. Analysis of follicular fluid and serum markers of oxidative stress in women with infertility related to endometriosis. Fertil Steril. 2012;98:126–130.

12. Tinkanen H, Kujansuu E. In vitro fertilization in patients with ovarian endometriomas. Acta Obstet Gynecol Scand. 2000;79:119–122.

13. Loh FH, Tan AT, Kumar J, Ng SC. Ovarian response after laparoscopic ovarian cystectomy for endometriotic cysts in 132 monitored cycles. Fertil Steril. 1999;72:316–321.

14. Ho HY, Lee RK, Hwu YM, Lin MH, Su JT, Tsai YC. Poor response of ovaries with endometrioma previously treated with cystectomy to controlled ovarian hyperstimulation. J Assist Reprod Genet. 2002;19:507–511.

15. Roman H, Auber M, Mokdad C, et al. Ovarian endometrioma ablation using plasma energy versus cystectomy: a step toward better preservation of the ovarian parenchyma in women wishing to conceive. Fertil Steril. 2011;96:1396–1400.

16. Donnez J, Lousse JC, Jadoul P, Donnez O, Squifflet J. Laparoscopic management of endometriomas using a combined technique of excisional (cystectomy) and ablative surgery. Fertil Steril. 2010;94:28–32.

17. Kitajima M, Dolmans MM, Donnez O, Masuzaki H, Soares M, Donnez J. Enhanced follicular recruitment and atresia in cortex derived from ovaries with endometriomas. Fertil Steril. 2014;101:1031–1037.

18. Brosens I, Puttemans P, Gordts S, Campo R, Gordts S, Benagiano G. Early stage management of ovarian endometrioma to prevent infertility. Facts Views Vision Obgyn. 2013;5:309–314.

How to cite this article: Nakamura, M., Yamashita, Y., Hayashi, A., Saito, N., Yu, M., Hayashi, M., Terai, Y., and Ohmichi, M. (2017). Analyzing the risk factors for a diminished oocyte retrieval rate under controlled ovarian stimulation. Reproductive Medicine and Biology, 16: 40–44. doi: 10.1002/rmb2.12004.