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ORIGINAL ARTICLE

Investigation of an efficient method of oocyte retrieval by dual stimulation for patients with cancer

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Abstract

Purpose: To examine the optimal timing of second ovarian stimulation using the dual stimulation method for good ovarian responders with cancer undergoing oocyte retrieval for fertility preservation.

Methods: A retrospective analysis was conducted using data from 69 patients with cancer who underwent oocyte retrieval for fertility preservation at four Japanese institutions during 2010–2021. Twenty-two patients underwent two oocyte retrievals for fertility preservation. We studied the relationship between the initial number of oocytes retrieved via dual stimulation and risk of ovarian enlargement as well as the appropriate waiting interval between the end of the first ovarian stimulation and beginning of the second ovarian stimulation.

Results: The risk of ovarian enlargement was high when the initial number of oocytes retrieved via dual stimulation was ≥5. An 8-day waiting interval may be more effective for performing a second ovarian stimulation oocyte retrieval in these cases, although the difference was not significant.

Conclusions: This study provides one policy for effectively managing ovarian enlargement and timing of second ovarian stimulation during oocyte retrieval via the dual stimulation method for patients with cancer undergoing fertility preservation. If more facilities implement this procedure, more oocytes may be obtained in a short period for fertility preservation purposes.

KEYWORDS
cryopreservation, dual stimulation, oncofertility, waiting period

Attestation statement: The subjects in this trial have not concomitantly been involved in other randomized trials. Data regarding any of the subjects in the study have not been previously published unless specified. Data will be made available to the editors of the journal for review or query upon request.

Capsule: An 8-day waiting interval after the first ovarian stimulation with at least five oocytes retrieved may lead to good results of dual stimulation for patients with cancer with good ovarian response.

1 | INTRODUCTION

The number of cancer survivors has been increasing owing to improved cancer treatment outcomes.[1,2] However, chemotherapy and radiotherapy can severely impair gonadal function in some cases. Therefore, many patients request fertility preservation before cancer treatment.[3] Options include sperm cryopreservation for men, ovarian tissue cryopreservation for girls, and ovarian tissue cryopreservation and unfertilized oocyte and embryo cryopreservation for young women.[4] Ovarian tissue cryopreservation is used worldwide, and the number of pregnancies after its implantation gradually increases, demonstrating its effectiveness.[5–7]

Various ovarian stimulation methods, including random start[8–11] and dual stimulation,[10–13] can minimize the impact of ovarian stimulation on the timing of cancer treatment initiation. For the random start method, ovarian stimulation is initiated by injections of follicle-stimulating hormone (FSH) and other substances regardless of the menstrual cycle; therefore, it is very beneficial for patients who are about to begin cancer treatment as it shortens the duration of ovarian stimulation. Good oocytes and embryos can be obtained without affecting embryo quality, even if ovarian stimulation is initiated before menstruation.[13] The dual stimulation method, in which two oocyte retrievals are performed in one menstrual cycle, ensures a sufficient number of oocytes even in the second oocyte retrieval, shows no difference in pregnancy results between the first and second oocyte retrieval, and has no effect on embryo quality.[13] The dual stimulation method has also been used in cases of poor ovarian responders with good results.[14,15] In this study, we defined a poor responder as a case that meets the Bologna criteria[15] and a good responder as any other case where the ovary responds well to the ovarian-stimulating hormone. For patients with cancer, the dual stimulation method is usually performed in good responders[11] but frequently results in ovarian hyperstimulation syndrome (OHSS) after the first oocyte retrieval procedure.[16] This can lead to reluctance to start the second oocyte retrieval using ovarian stimulation, and the delay may have potential consequences for the scheduling of subsequent chemotherapy. We have encountered cases of inadequate follicle development even in the absence of severe OHSS and with injections of FSH or human menopausal gonadotropin (HMG) when the ovaries are enlarged owing to numerous luteinized follicles. In such cases, waiting for ovarian shrinkage to a certain size before starting injections will result in good follicle development; however, no reports have examined the relationship between the status of ovarian enlargement and the timing of injections.

Therefore, in this retrospective analysis based on data on oocyte retrieval cases using the dual stimulation method, we aimed to assess the following two main topics: the status of ovarian enlargement and timing of injections. We examined the validity of the first oocyte retrieval count as an indicator of ovarian enlargement and evaluated the appropriate waiting interval between the end of the first ovarian stimulation and beginning of the second ovarian stimulation. We also analyzed the difference in the results of oocyte retrieval between patients with only one ovarian stimulation and those with dual stimulation and the difference in the results of oocyte retrieval during the first and second retrieval in individuals with dual stimulation.

2 | MATERIALS AND METHODS

2.1 | Ethical approval and study design

The Ethics Committee of Mie University Hospital approved this study (approval number: H2023-061). This study was conducted between January 2010 and March 2021 at four institutions (Mie University Hospital, St. Marianna University Hospital, Shiga University Hospital, and Saitama Medical Center) in patients who were diagnosed with cancer, received an explanation about fertility preservation before starting chemotherapy, and requested unfertilized oocyte or embryo cryopreservation (Figure 1). Ovarian stimulation was initiated using the random start[8] or short method.[17] The procedure was terminated after one retrieval for patients whose first oocyte retrieval either ensured a sufficient number of oocytes or did not wish to undergo more than one oocyte retrieval. Patients with insufficient oocytes or embryos from the initial retrieval requested a second ovarian stimulation. This was performed using either the antagonist or mild stimulation method (Figure 1). In this study, such cases were referred to as dual stimulation cases (DSC), where the second ovarian stimulation was initiated after the first oocyte retrieval and before the onset of menstruation. Figure 1 shows the dual stimulation timeline from the start of the first ovarian stimulation to the end of the second retrieval. The oocyte retrieval was performed 2 days after the end of the stimulation, and this interval was ignored in this study. The first and second stimulation periods are denoted by SP1 and SP2, respectively. Additionally, the waiting interval between the end of the first retrieval and start of the second stimulation is denoted by WI. Cases where the second ovarian stimulation was not performed for some reason are called single stimulation cases (SSC). For SSC, the stimulation period is also denoted by SP1. The choice of each ovarian stimulation method in dual stimulation was based on each institution's criteria, including patient age, follicle count, and anti-Mullerian hormone (AMH) level. Because this was a multicenter, retrospective study, some centers did not measure AMH values or ovarian diameter after oocyte retrieval and were excluded from the present endpoints.

2.2 | Considerations and analysis methods

The following four points were considered in this study:

2.2.1 | Comparison of initial ovarian stimulation results between patients with only one ovarian stimulation and those with dual ovarian stimulation, and comparison of first and second ovarian stimulation results in those with two ovarian stimulations

In fertility preservation, if a sufficient number of oocytes cannot be obtained by one oocyte retrieval, a second oocyte retrieval is performed (i.e., DSC). We examined the relationship between oocyte

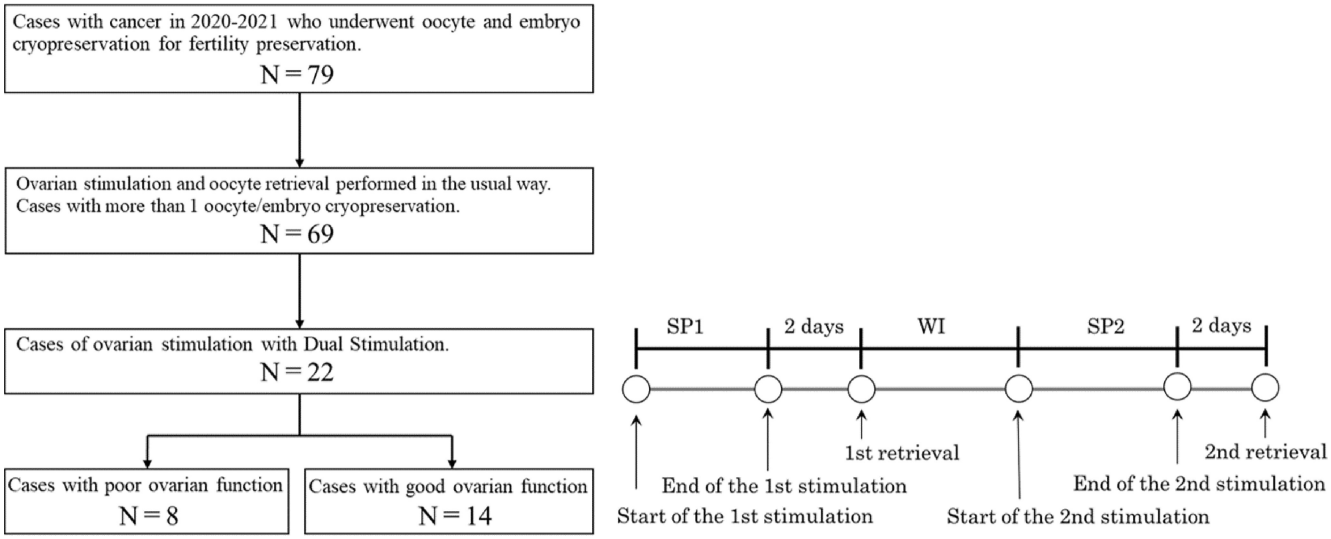

FIGURE 1 Description of the cases and timeline covered in this study: patients with cancer in 2020–2021 where fertility preservation was desired and oocyte/embryo cryopreservation was performed. Ovarian stimulation was performed in 69 and 22 patients using the usual method and dual stimulation, respectively. Of the 22 individuals, 8 and 14 had poor and good ovarian function, respectively. At least one ovary was cryopreserved. The timeline from the start of the first ovarian stimulation to the end of the second ovarian stimulation in the dual stimulation method was as follows: SP1, 1st stimulation period; WI, waiting interval; and SP2, 2nd stimulation period.

retrieval in the first cycle of DSC and that in SSC. Additionally, sufficient oocytes should be obtained in DSC. Thus, to ensure this, past reports have indicated that the second oocyte retrieval should have the same or a higher number of oocytes retrieved and matured oocytes than the first oocyte retrieval. Therefore, to examine the effectiveness of the second oocyte retrieval, the oocyte retrieval in the first and second cycles in DSC was compared. This analysis compared the mean values of total FSH and HMG injections, duration of ovarian stimulation, number of oocytes retrieved, and number of matured oocytes in each group. The Mann–Whitney *U* test was used to assess differences in means, where the risk rate of 0.05 indicated a significant difference.

2.2.2 | Study of the influence of the number of oocytes retrieved in the first ovarian stimulation on the second ovarian stimulation in DSC

We first evaluated the validity of using the number of oocytes retrieved after the first stimulation (NOR1) to indicate ovarian enlargement for DSC. Ovarian enlargement may occur depending on the number of developing follicles, which can result in unresponsiveness to gonadotropic hormone injections and delayed follicle development. Thus, if ovarian enlargement occurs after the first oocyte retrieval, a longer WI is set before the start of the second ovarian stimulation based on the reproductive specialist's discretion (Figure 1). However, if this is insufficient, SP2 may be prolonged. In contrast, if the number of developing follicles is low and the ovaries are not enlarged after oocyte retrieval, WI and SP2 are shorter. Unfortunately, this study cannot directly confirm this relationship because the number of cases where the ovarian diameter was measured after the first oocyte retrieval was small. However, since NOR1 is also used to assess the risk of OHSS, a higher NOR1 is known to be associated with a greater risk of ovarian enlargement.[18] Existing reports have indicated that the moderate OHSS group, which had a higher number of oocytes retrieved, had significantly larger ovaries than the mild OHSS group, which had a lower number of oocytes retrieved.[18] NOR1 may reflect a situation of ovarian enlargement, and it is obtained in our treatments. More precisely, we hypothesized that if a change point exists on NOR1 at which WI + SP2 jumps and WI + SP2 is shorter/longer before and after the change point, then NOR1 could be considered an indicator of ovarian enlargement that determines the WI.

We performed the Buishand range test to detect the change point.[19] The R function br.test in the "trend" package was used for change point detection. In the br.test, the standardized CUSUM (CUMulative SUM) was used as the test statistic, and the *p*-value was calculated using the Monte Carlo calculation under the assumption of sample normality.

2.2.3 | Start timing of the second ovarian stimulation in DSC

In this study, we examined the appropriate WI for DSC with ovarian enlargement following the first stimulation. Such cases were determined according to the change point detection in 2.2.2, where WI + SP2 was long.

In DSC, if the ovaries are enlarged after the first ovarian stimulation, a long WI is needed before the start of the second ovarian stimulation. If WI is prolonged, it may affect the initiation of cancer treatment. Conversely, if WI is relatively short, the ovaries may respond poorly to

the injections, prolonging the duration of the second ovarian stimulation, which may result in an excessive physical and economic burden for the patient. Therefore, an appropriate WI should be established.

SP1 is the patient's original follicular development period unaffected by prior medications; however, SP2 may be affected by the first ovarian stimulation. If there is no effect, the duration of the second ovarian stimulation is the same as the first. However, if there is an effect, there may be a difference between the two periods (i.e., SP2–SP1). Typically, a longer WI decreases the difference between SP1 and SP2, approaching zero. In such a situation, if there is a WI value at which SP2–SP1 changes (decreases) abruptly, the effect of the first ovarian stimulation is considered greater before this WI value and lessened after it. Therefore, by employing such a waiting interval, the effect of the first ovarian stimulation can be reduced to some extent, and the disadvantages of a longer waiting period can be avoided.

We aimed to detect the change point in the relationship between WI and SP2–SP1. If a change point on WI at which SP2–SP1 jumps existed and SP2–SP1 was larger/smaller before and after the change point, such a WI may have been an appropriate interval. We used the Buishand range test to detect the change point. The R function br.test in the "trend" package was used for the change point detection. In the br.test, the standardized CUSUM was used as the test statistic, and the *p*-value was calculated using the Monte Carlo calculation under the assumption of sample normality.

3 | RESULTS

3.1 | Study participants

The study included 69 patients with a mean age of 34.3 (20–42) years. Among them, 22 patients with a mean age of 34.3 years (26–41) underwent two oocyte retrievals (Figure 1).

3.2 | Results of ovarian stimulation in cases with only one ovarian stimulation and those with dual stimulation

Figure 2 shows the mean values for the total FSH and HMG injection doses, duration of ovarian stimulation, number of oocytes retrieved, and number of matured oocytes in SSC and DSC. The total SSC injection dose was 2264.6 ± 788.0 mIU/mL (Figure 2A), and the stimulation period was 9.2 ± 2.2 days (Figure 2B). The total dose for the first and second injections in DSC was 2042.0 ± 470.0 mIU/mL (Figure 2A,E) and 2312.5 ± 878.0 mIU/mL (Figure 2E), respectively. The duration of stimulation for the first and second DSC was 8.5 ± 1.8 days (Figure 2B,F) and 8.6 ± 3.8 days (Figure 2F), respectively.

The mean number of retrieved and matured oocytes in SSC was 15.1 ± 11.8 (Figure 2C) and 11.1 ± 8.1 (Figure 2D), respectively. In the first stimulation of DSC, the numbers of retrieved and matured oocytes were 7.5 ± 5.6 (Figure 2C,G) and 5.3 ± 3.9 (Figure 2D,H), respectively; in the second stimulation, these numbers were 9.9 ± 6.6 (Figure 2G) and 9.4 ± 6.1, respectively (Figure 2H).

The Mann–Whitney *U* test was used to determine whether a difference existed in the means of each observation. Therefore, in the comparison in Figure 2, a $p < 0.01$ was for the number of oocytes retrieved and matured oocytes between SSC and the first stimulation in DSC, a $p < 0.05$ was for the number of matured oocytes between the first and second stimulations in DSC, and the difference was considered statistically significant.

3.3 | Assessment of ovarian enlargement after the first oocyte retrieval affecting the second ovarian stimulation

Figure 3 shows a scatter plot with NOR1 on the horizontal axis and WI + SP2 on the vertical axis.

Here, the Buishand range test was applied to detect the change point of the mean of the WI + SP2 on NOR1. A change point was detected between the retrieved oocyte counts of 3 (9th sample) and 5 (10th sample). As the *p*-value was $<2.2 \times 10^{-16}$, this change point was valid. The mean values in the WI + SP2 period of ≤3 and ≥5 were 7.778 and 20.786, respectively. These mean values are shown in Figure 3 as horizontal lines superimposed on the data. If the number of oocytes retrieved is small, the ovaries are not enlarged. Therefore, follicles form in the typical follicle development period even if ovarian stimulation is initiated immediately after oocyte retrieval. When the number of oocytes retrieved is high, the ovaries are enlarged, similar to that in OHSS, the ovarian response to ovarian stimulation is poor, and follicle development is delayed than normal. When the number of oocytes retrieved was ≤3, WI + SP2 was short, leading to a second oocyte retrieval. This indicated that there were no factors, such as ovarian enlargement, which inhibited the effect on follicle development. Nonetheless, when the number of oocytes retrieved was ≥5, WI + SP2 was significantly longer, suggesting that either the second follicle stimulation took longer owing to ovarian enlargement or WI before the start of the second ovarian stimulation was required in anticipation of ovarian shrinkage. Based on these results, we inferred that cases of ovarian enlargement affecting the second ovarian stimulation were those where the number of oocytes retrieved in the first cycle was ≥5.

3.4 | Optimal period for the start of the second ovarian stimulation after the first oocyte retrieval in the dual stimulation

In DSC, WI is considered, particularly for patients affected by ovarian enlargement. Based on the abovementioned results, the cases for which NOR1 was ≥5 were considered target cases. The relationship between WI and SP2–SP1 was also considered. There were 14 such patients, with a mean age of 34.4 (26–41) years.

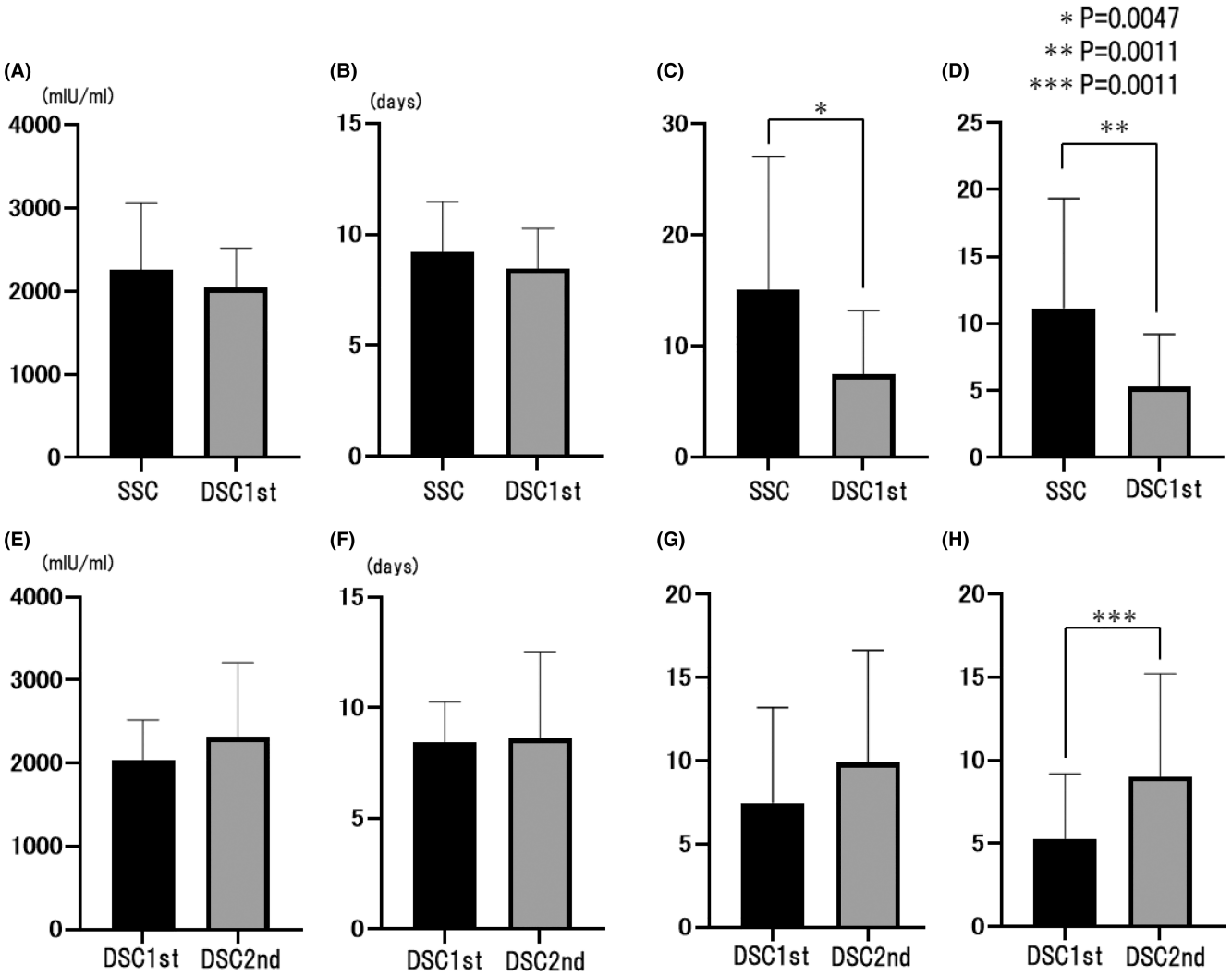

FIGURE 2 Comparison of ovarian stimulation results between single stimulation cases (SSC) and the first cycle in dual stimulation cases (DSC) and between the first and second cycles in DSC. (A) Total injection dose (SSC vs. DSC 1st), (B) ovarian stimulation period (SSC vs. DSC 1st), (C) the number of oocytes retrieved (SSC vs. DSC 1st), (D) the number of matured oocytes (SSC vs. DSC 1st), (E) total injection dose (1st vs. 2nd in DSC), (F) ovarian stimulation period (1st vs. 2nd in DSC), (G) the number of oocytes retrieved (1st vs. 2nd in DSC), and (H) the number of matured oocytes (1st vs. 2nd in DSC). No significant differences were found between SSC and first-cycle DSC regarding injection dose and duration of ovarian stimulation. However, the number of retrieved and matured oocytes was predominantly higher in the SSC. Only the number of matured oocytes was predominantly higher in the second DSC than in the first DSC.

Figure 4 shows a scatter plot with WI and SP2–SP1 on the horizontal and vertical axes, respectively. Furthermore, we used the previously described method to determine if there was a change point in SP2–SP1. A change point was detected between intervals 7 (third sample) and 8 (fourth sample), while its *p*-value of 0.3 was not necessarily significant. The mean values for ≤7 days and ≥8 days were 5.667 and 0.818, respectively. These mean values are shown in Figure 4 as horizontal lines superimposed on the data. Currently, the number of samples (especially when the WI is short) is considered relatively small to indicate the presence of a change point. However, if the detected change points were considered reasonable, an 8-day waiting interval would be needed for a stable retrieval in the second cycle for cases where more than five oocytes were retrieved in the first oocyte retrieval.

4 | DISCUSSION

For young patients with cancer who wish to preserve their fertility, preserving sufficient fertile specimens to allow future pregnancies and avoiding delays in the initiation of cancer treatment are crucial. Therefore, reproductive specialists require a method that can preserve sufficient fertility specimens in a short time. The random start and dual stimulation methods are suitable. Oocyte and embryo cryopreservation requires a certain period for ovarian stimulation[20]; however, a second oocyte retrieval is frequently attempted if sufficient oocytes cannot be secured after one oocyte retrieval. Acquiring many oocytes can cause OHSS, where the ovaries enlarge. However, there are many cases of ovarian enlargement without the presence of ascites or pleural effusion. In in vitro fertilization, the

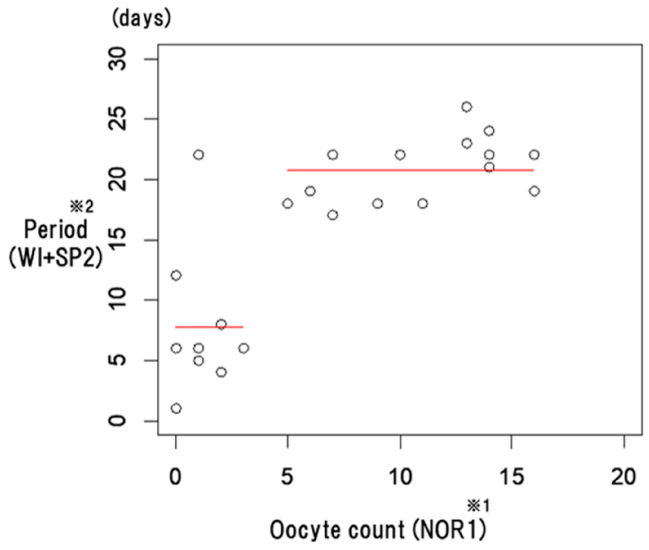

FIGURE 3 Comparison of the number of oocytes retrieved in the first cycle and the time between the first and second oocyte retrieval in cases of dual stimulation use. ※1: Number of oocytes retrieved in the first cycle (NOR1), and ※2: the period from the first oocyte retrieval to the second oocyte retrieval (WI + SP2): when the number of oocytes retrieved was ≤3, the waiting interval was short and the second oocyte retrieval was accomplished in a short time. However, when the number of oocytes retrieved was ≥5, either the second follicle stimulation took longer or the waiting interval to start the second ovarian stimulation was longer.

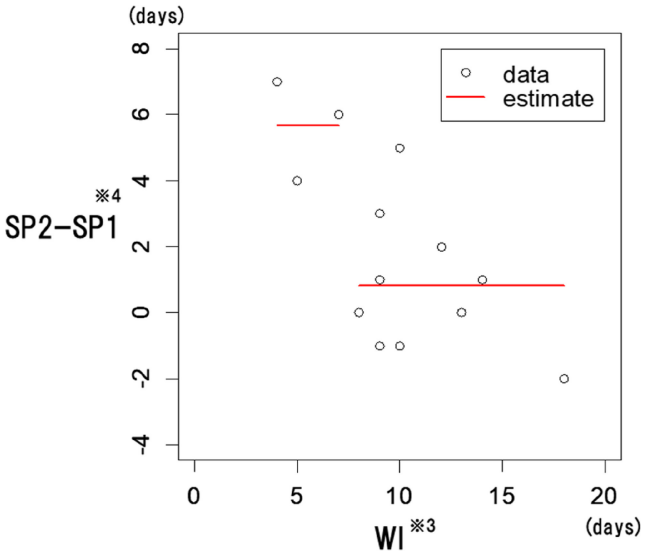

FIGURE 4 Estimated difference and mean number of days of ovarian stimulation relative to the interval. ※3: The number of days between the first oocyte retrieval and the start of the second ovarian stimulation (waiting interval: WI), and ※4: the difference between the number of days of the second ovarian stimulation and that of the first (SP2–SP1): patients with a waiting interval of ≤7 days had a longer second ovarian stimulation period, while those with a waiting interval of ≥8 days did not have a prolonged second ovarian stimulation period.

next stimulation cycle is typically started after menstruation has begun and the ovaries have shrunk. Conversely, for patients with cancer, waiting for the next stimulation cycle may delay the start of cancer treatment; therefore, a second stimulation cycle may be initiated without waiting for the ovaries to shrink.

The pregnancy rate per cryopreserved oocyte is reportedly low, at 4.5%–12%[21]; therefore, cryopreservation of a large number of oocytes is desirable. Cobo et al. reported that for a 40%–70% chance of future pregnancy, a 35-year-old patient should have 10–15 frozen oocytes.[22] Oocyte retrieval is an invasive procedure involving a transvaginal needle puncture after daily injections. Many patients proceed directly to cancer treatment if a sufficient number of oocytes can be obtained in a single oocyte retrieval. In this study, patients who requested two ovarian stimulation cycles also had fewer oocytes retrieved and fewer matured oocytes in the first cycle than those who completed only one cycle (Figure 2). Even among good responders, the number of follicles that develop after a single ovarian stimulation varies from approximately 7 to more than 20, depending on ovarian function and the antral follicle count at the start of stimulation.

In DSC, the number of oocytes retrieved in the first and second cycles was comparable (Figure 2). The number of matured oocytes was significantly higher for those retrieved in the second cycle (Figure 2). Previous reports found no significant difference in oocyte retrieval and maturity between the first and second dual stimulation cycles[13] and demonstrated a higher yield of oocytes in the second ovarian stimulation.[23] Our results support the higher yield of oocytes in the second ovarian stimulation. Regarding pregnancy rates, the existing reports have shown no difference between the first and second ovarian stimulations,[13] and the dual stimulation method was considered very useful in young patients with cancer.

Despite recent reports[10,11,13–15,19] on dual stimulation, none mention the period between the first oocyte retrieval and start of the second ovarian stimulation. Even after oocyte retrieval, many ovaries remain normal-sized in poor ovarian responders. Therefore, even if ovarian stimulation is initiated immediately after oocyte retrieval, follicle development can be expected. However, in good ovarian responders, the ovaries may enlarge after oocyte retrieval, resulting in OHSS-like ovaries (ovarian enlargement of at least 6 cm owing to numerous corpus luteum). The only existing report on cases of ovarian enlargement after oocyte retrieval is the risk criteria for the development of OHSS,[16] and the results can only be used as an indicator for therapeutic intervention. Nevertheless, some cases of ovarian enlargement require no therapeutic intervention, and many do not respond to FSH or other therapies. Therefore, the relationship between ovarian enlargement and waiting interval (from oocyte retrieval to the start of the second ovarian stimulation) should be examined. Noting that the number of first oocytes retrieved may indicate the degree of ovarian enlargement, we examined the relationship between the "number of first oocytes retrieved" and "time between the first oocyte retrieval and the end of the second ovarian stimulation period." As shown in Figure 3, a significant difference was found in the "time from the first oocyte retrieval to the end of the second ovarian stimulation" between the retrieval of oocytes

≤3 and that of those ≥5, demonstrating the statistical significance of this difference. Given that the difference in "the time between the first oocyte retrieval and the end of the second ovarian stimulation" is influenced by ovarian enlargement, the number of oocytes retrieved in the first cycle reflects the effect of ovarian enlargement. Therefore, a certain waiting interval should be allowed before the start of the second ovarian stimulation if the number of oocytes retrieved in the first cycle is ≥5.

In practice, the question is how long a waiting interval is required when the ovaries are enlarged. Specifically, suppose the difference between the second and first ovarian stimulation periods is almost the same. In such a case, the second ovarian stimulation is considered to be unaffected by the first cycle, and the idea was to use this difference as an indicator to examine an appropriate waiting interval. The relationship between the waiting interval and difference between the two periods is shown in Figure 4. Although a method detected a change point between the 7th and 8th days of the waiting interval, the statistical significance of the detection was unclear. Therefore, we need more samples to determine an optimal waiting interval. This result indicates that a waiting interval of approximately 8 days before the start of the second ovarian stimulation can reduce the impact of the first ovarian stimulation. However, this result is not statistically significant owing to the small sample size. Therefore, a limitation of this study is that future analysis with a larger sample size is needed.

In conclusion, dual stimulation has been widely used in poor ovarian responders, and this method is being utilized in good ovarian responders with cancer to maximize the preservation of oocytes. However, waiting intervals may be needed to reduce the chance of OHSS. The results of this study also indicate that follicles develop even before menstruation if a certain time is allowed to pass after the first oocyte retrieval, depending on the ovarian function and the number of oocytes initially retrieved. Nonetheless, more data from different centers are needed to strengthen these findings and support shorter wait times for fertility preservation.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

HUMAN RIGHTS STATEMENTS AND INFORMED CONSENT

All procedures followed were 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 patients for being included in the study.

ETHICAL APPROVAL

The Ethics Committee of Mie University Hospital approved this study (approval number: H2023-061).

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