Mild Stimulation Cycles versus Controlled Stimulation Cycles: A Japanese Perspective

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Abstract

The aim of assisted reproductive technology (ART) is to achieve the best clinical results in a single treatment. Historically, controlled stimulation has been routinely carried out under the concept that the more oocytes utilized, the higher is the success rate. Recently, mild stimulation protocol has gathered attention because of its simplicity and easiness. It consists of 100 mg of Clomiphene plus 1–2 shots of follicle-stimulating hormone (FSH) or human menopausal gonadotropin (hMG), so no gonadotropin-releasing hormone (GnRH) agonist nor GnRH antagonist with 6–8 shots of FSH or hMG are necessary. If the clinical outcome following a mild stimulation is not significantly different from that of the controlled stimulation method, this mild stimulation method might be the first choice for ART patients. Now, the optimal number of collected oocytes can be controlled by choosing an appropriate stimulation method. Using the latest available techniques, we can now develop 10–15 oocytes without significant stress for patients with an individualized stimulation method. Controlled stimulation showed higher success rates compared to those of mild stimulation regardless of the number of ampules of hMG used or the number of oocytes collected in mild stimulation. These differences became more prominent in the group of older patients (over 34 years old and less than 40 years old), which is the age group where ART is most relevant. The main goal for Reproductive Medicine specialists should therefore be to find the best stimulation protocol through individualization to match the particular needs of the patient.

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G.N. Allahbadia, Y. Morimoto (eds.), *Ovarian Stimulation Protocols*,
DOI 10.1007/978-81-322-1121-1_7

Keywords
ART • Mild stimulation • Controlled stimulation • Accumulation pregnancy rate

Introduction

The history of ART is closely related to that of ovarian stimulation.

In vitro fertiilization and embryo transfer (IVF-ET) is now an established method for treating female infertility. The first successful pregnancy resulting from IVF-ET occurred following an unstimulated normal menstrual cycle [1]. However, following the extensive use of ovarian stimulation by exogenous follicle-stimulating hormone (FSH) to obtain more oocytes [2–4], treatment options using the natural cycle have been almost completely abandoned. This has resulted in fewer cancelled cycles and improved pregnancy rates, especially when downregulation with gonadotropin-releasing hormone (GnRH) analogs prior to ovarian stimulation is employed [5].

A long GnRH agonist pituitary suppression regimen, combined with relatively high doses of exogenous FSH, remains the most frequently used stimulation protocol [4, 6]. This method, referred to as the controlled stimulation (CS), promotes better clinical outcomes but is also associated with a high risk of ovarian hyperstimulation syndrome (OHSS) [7–9] and multiple births. On the other hand, the mild stimulation method (MS) is based on the administration of Clomiphene [2, 3, 10] and reduces the risks associated with CS. These two methods are the leading protocols of ovarian stimulation at present, although the mild stimulation method aims to be a safer, more patient-friendly protocol in which the risks of stimulation are minimized [7, 11–16].

The aim of this chapter is to compare the conventional controlled ovarian hyperstimulation (COH) method with the mild stimulation method, from a Japanese perspective. In 2011, Japan reported the largest number of ART cycles performed (161,980) [17] and the largest number of ART institutions (650) [17] in the world. Consequently, the present article has significant global relevance.

We conducted a randomized prospective study at 18 member institutions of JISART (Japanese Institution for Standardizing Assisted Reproductive Technology). A large number of papers have been published in the last 10 years, addressing natural and mild approaches to IVF [18, 19]. Recent studies have addressed the potential advantages of modified natural cycle and mild IVF in the light of current attempts to reduce patient distress, multiple births, and the cost of IVF cycles [18, 19]. It is not so easy to compare these two protocols across different countries due to differences in governmental financial support, in terms of the technical level of embryo cryopreservation [20, 21] and in terms of supporting neonatal intensive care unit systems and ethical issues [22]. This study, therefore, was conducted based only on Japanese data.

Is Mild Stimulation ART Patient-Friendly?

The ISMAAR (International Society for Mild Approaches in Assisted Reproduction) defines mild IVF cycle as the method used when FSH or hMG is administered at lower doses, and/or for a shorter duration in a GnRH antagonist co-treated cycle, or when oral compounds (anti-estrogens, or aromatase inhibitors) are used [23], either alone or in combination with gonadotropins to reduce the number of collected oocytes to between 2 and 7 [24]. In this definition, the kind of stimulation medication used does not matter, whether it is a GnRH agonist or GnRH antagonist [25–27], and the hMG units remains irrelevant as long as the number of collected oocytes is between 2 and 7 [19, 24]. From the patient's

point of view, the term "mild" is commonly associated not with the number of collected oocytes, but rather, with how hard the process of ovarian stimulation will be upon them. Patient stress is derived from the number of hMG injections, the number of developed oocytes, and the method of luteal support. In order to reduce the burden upon patients, it is imperative that we take these factors into consideration. Mild stimulation, performed in Japan, is defined as a low-dose stimulation that is based only on the administration of Clomiphene with 1–2 injections of hMG or FSH. However, in practice, more than 3 injections of hMG/FSH are sometimes used, and a GnRH antagonist [28] is occasionally, also used to control the LH surge. In these cases, there is little observed difference with regular stimulation. We therefore, believe that a more detailed definition of the term "mild stimulation" should be established.

The results of an unpublished questionnaire, collected at Saint Mother Hospital, showed that the main reason for patients dropping out from infertility treatment was the financial burden it causes. The second cause was psychological stress caused by frequent unsuccessful trials, which then resulted in serious financial burden [29, 30]. Judging from these results, what is most needed for ART patients is to reduce the financial burden [31]. Patients want to become pregnant in the least possible number of trials [22, 32–34]. Stimulation medicine, or anesthesia during oocyte pick-up, is not a significant problem for them.

Recently, the burden of ART caused by controlled stimulation, has been reduced thanks to self-injection, the development of techniques to count the number of antral follicles, and measurements of anti-Mullerian hormone (AMH) in advance, which make the prediction of OHSS easier. These advances make the selection of optimal methods of ovarian stimulation, based on these predictive findings, possible [35]. Nowadays, the physical and psychological burden following controlled ovarian stimulation is not likely to be as severe as it was before. Such advances in CS techniques reduce and, in some cases, eliminate the advantages that MS offers [36].

Comparison of Mild and Controlled Ovarian Stimulation Methods in Japan

Eighteen ART institutions conducted a randomized prospective study to compare the clinical results of mild and controlled stimulation in Japan. Patients were divided by age into two groups, younger than 35 years old (referred to as the "younger group") and between 35 and 39 years old (referred to as the "older group"). We analyzed clinical outcomes of mild and controlled stimulation methods from three points of view, as detailed below:

1. A comparison of results between the two groups according to fresh embryo transfer or frozen-thawed embryo transfer (FET).
2. A comparison of clinical results in the mild stimulation group according to the units of hMG used (two or less 150 IU ampules versus 3 or more 150 IU ampules)
3. A comparison of pregnancy rates per cycles versus per transfers.

The main findings of these comparisons are presented in the following tables (Tables 7.1 and 7.2).

In Table 7.1, there were statistically significant differences in the results obtained from each method, and they indicate that CS was more effective than MS in the older group following both of the fresh embryo transfer and the FET. There were no significant differences between CS and MS in the younger group following both the fresh embryo transfer and the FET.

In Table 7.1, the results show that statistically significant differences were found between mild stimulation when two or less ampules were used (MS $\leq$2A) and CS in both age groups after fresh embryo transfer. Statistically significant differences were found between CS and MS in the older group when three ampules or more of hMG (3A hMG) were used after frozen-thawed embryo transfer.

When looking at a pregnancy rate, we need to assess whether it is calculated per cycle or per transfer. Our data showed no significant

Table 7.1 Clinical results in mild stimulation or controlled stimulation

		Method			
		Fresh embryo transfer		Frozen-thawed embryo transfer	
Age		MS	CS	MS	CS
≤34	Pregnancy rates (per cycle)	22.7 % (17/75)	34.9 % (37/106)	55.8 % (24/43)	53.2 % (50/94)
	Miscarriage rates	23.5 % (4/17)	24.3 % (9/37)	25.0 % (6/24)	14.3 % (7/49)
≥35 ~ ≤39	Pregnancy rates (per cycle)	10.3 % (10/97)*	34.2 % (52/152)*	20.4 % (11/54)*	42.7 % (35/82)*
	Miscarriage rates	10.0 % (1/10)	28.8 % (15/52)	27.3 % (3/11)	22.9 % (8/35)

*$P<0.05$

Table 7.2 Clinical results in mild stimulation group according to units of hMG (150 IU × ≤ 2A vs. 150 IU × ≥ 3A) or controlled stimulation

		Method					
		Fresh embryo transfer			Frozen-thawed embryo transfer		
Age		≤2A	≥3A	CS	≤2A	≥3A	CS
≤34	Pregnancy rates (per cycle)	10.0 % (3/30)*	31.1 % (14/45)	34.9 % (37/106)*	45.5 % (5/11)	59.4 % (19/32)	53.2 % (50/94)
	Miscarriage rates	33.3 % (1/3)	21.4 % (3/14)	24.3 % (9/37)	20.0 % (1/5)	26.3 % (5/19)	14.3 % (7/49)
≥35 ~ ≤39	Pregnancy rates (per cycle)	6.3 % (3/48)*	14.3 % (7/49)	34.2 % (52/152)*	20.0 % (2/10)	20.5 % (9/44)*	42.7 % (35/82)*
	Miscarriage rates	0.0 % (0/3)	14.3 % (1/7)	28.8 % (15/52)	0.0 % (0/2)	33.3 % (3/9)	22.9 % (8/35)

*$P<0.05$

differences in per cycle pregnancy rate when compared between mild stimulation and controlled stimulation. However, for ART patients, what is most relevant is not the number of transfers but the number of cycles needed to acquire a successful pregnancy. The pregnancy rate should be presented not per transfer, but per cycle, including the number of cancelled cycles [18, 37]. Data at the clinic, which reported the largest number of cycles in Japan showed that a pregnancy rate of 32.3 % [37, 38], when calculated per transfer, decreased to 16.6 % when calculated per cycle.

Decision Tree Analysis as a Tool to Identify an Optimal Ovarian Stimulation Method

The skill that is most requested from Reproductive Medicine experts is the ability to choose the optimal ovarian stimulation protocol that will lead to the development of an appropriate number of high quality oocytes [10–15]. Each patient has a different background, which strongly influences the clinical outcome. Factors, such as age, height, body weight, AMH level, past chronic diseases, the number of antral follicles, and the measurement of serum estradiol (E2), LH, and FSH levels on the third day of the menstrual period all affect the outcome. Essentially, this means that the ovarian stimulation regimen should be individualized after taking these factors into consideration. The novel application of decision tree analysis [39] to ART treatments can help us identify the optimal stimulation method. Decision tree analysis is commonly used in statistics, data mining, and machine learning and uses a decision tree as a predictive model, which maps observations about an item to conclusions about the item's target value. Such an analysis can be successfully applied to ART treatment decisions (Fig. 7.1).

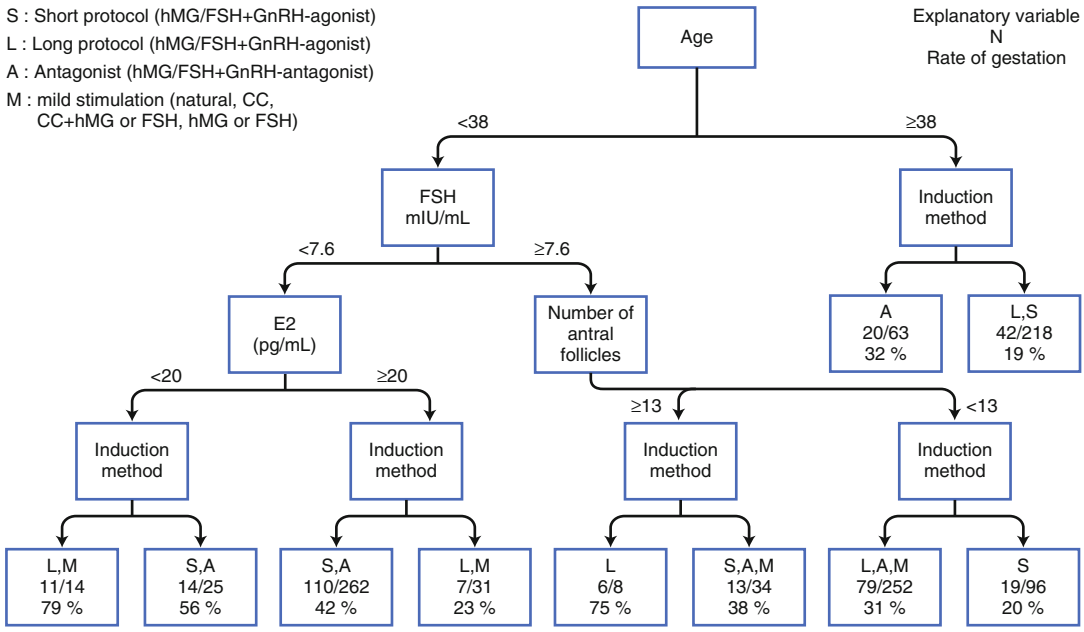

Fig. 7.1 Decision tree analysis for the selection of ART treatment

Discussion

We have investigated mild stimulation and controlled stimulation protocols in Japan. Clinical results for controlled stimulation showed a statistically significant difference for fresh embryo transfers, particularly in the 35–39 years age group, which represents the group with the most treatment cycles. This difference was more prominent when a dose of two or more injections (150 units) of FSH or hMG was used. Data suggests that the difference between the two methods is even greater when cumulative pregnancy rates are compared [40, 41].

Birth rate in Japan has sharply declined and currently sits at a figure of 1.4. This low birth rate has become a major social problem. It is considered that 2 % of all births are now achieved through infertility treatment, and this rate is expected to increase further. Therefore, the performance of ART treatments not only represents a personal issue but is also an important issue for Japan in general.

The selection of the specific ovulation induction method that leads to the best results is the most important task for clinicians. We used the same protocol in 18 facilities and conducted a comparative study between mild stimulation and controlled stimulation protocols. No significant difference was observed in the age group younger than 34 years old. We then divided mild stimulation protocol data into two groups (two or less, and three or more FSH or hMG ampule injections). It was found that mild stimulation, when defined as having two or less injections, was less effective than controlled stimulation.

In order to compare CS and MS objectively, we need to consider pregnancy rates not only per transfer but also per cycle as well as their relative cost performance. This is because patients wish to achieve a pregnancy in the lowest possible number of cycles [33, 42]. The cost performance of MS has been overlooked in Japan due to the fact that government subsidies are the same, regardless of the method used. In countries with more limited government support, the cost-effectiveness of the method is much more relevant.

An early pregnancy reduces the physical, psychological, and financial burden upon the patients [30]. The pregnancy rates for fresh embryo transfer and FETs in Japan (Saito H, 2010) are 21.9 %

and 32.7 %, respectively. FET exhibits a significantly higher pregnancy rate than the other two methods and is expected to become the standard method for ART in the future. As advanced techniques for freezing embryos have been developed, single embryo transfers have been established and the risk of multiple pregnancies has almost disappeared. In addition, the growing follicle number can be predicted more accurately, and the antral follicle number [43], E2 [44], LH, FSH [45], and AMH [46, 47] can be measured before treatment, making individualization of the ovulation induction method to be used (tailor-made treatments) possible. Furthermore, it is not an exaggeration to say that when using the whole embryo freezing method, the possibility of OHSS has almost disappeared. Therefore, instead of limiting our choices and uniformly applying mild stimulation protocols in an attempt to reduce the growing follicle number, it seems clear that thorough analysis of patient background, and choosing the best individualized ovulation induction method, must be the main goal of all Reproductive Medicine specialists.

Acknowledgements The authors thank Dr. Y. Asada (Asada Ladies Clinic), Dr. M. Ishikawa (Ishikawa Clinic), Dr. S. Okamoto (Okamoto Woman's Clinic), Dr. Y. Odawara (Fertility Clinic Tokyo), Dr. H. Kamiya (Kamiya Ladies Clinic), Dr. M. Kinutani (Kinutani Women's Clinic), Dr. T. Kyono (Kyono ART Clinic), Dr. T. Kuramoto (Kuramoto Women's Clinic), Dr. M. Shiotani (Hanabusa Women's Clinic), Dr. Y. Nagata (Center for Reproductive Medicine, IVF NAGATA Clinic), Dr. N. Hayashi (Okayama Couple's Clinic), Dr. K. Furui (Clinic Mama), Dr. Y. Morimoto (IVF Namba Clinic), Dr. H. Yoshida (Yoshida Ladies Clinic ART Center), and Dr. H. Watanabe (Daigo Watanabe Clinic) for their participation in this study.

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