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Noritoshi Enatsu *

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Research Article

The Association Between Gonadotropin Dosage and Oocyte Retrieval Outcomes in in-vitro fertilization (IVF) Cycles

Noritoshi Enatsu*, Yihsien Enatsu, Kunihiro Enatsu, Ai Yamada, Yuri Mizusawa, Eri Okamoto, Shoji Kokeguchi, Hiroaki Shibahara, Masahide Shiotani

Hanabusa Women's Clinic, Sannomiya Central Building 7F, 1-1-2 Sannomiya-cho, Chuo-ku, Kobe city, Hyogo, Japan.

***Corresponding Author:** Noritoshi Enatsu, Hanabusa Women's Clinic, Sannomiya Central Building 7F, 1-1-2 Sannomiya-cho, Chuo-ku, Kobe city, Hyogo, Japan.

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Abstract:

Background/Aim: To assess the relationship between Gonadotropin dosage and IVF outcomes, aiming to determine the optimal dosage for maximizing the IVF outcomes.

Materials and Methods: A detailed analysis was undertaken on 53,764 stimulation cycles conducted between January 2009 and May 2024. The primary endpoints encompassed the number of oocytes retrieved and secondary outcome was the number of blastocysts. Key parameters evaluated included the dosage of Gonadotropin, serum FSH concentrations stratified by patient age (<35, 35-40 and ≤40) and AMH categories (<1, 1-3 and 3≤).

Results: The analysis showed that increased total gonadotropin dosages affected the number of oocytes retrieved and blastocysts formed. Optimal outcomes were observed within the range of 2,000–3,000 IU, while efficacy decreased beyond this threshold. Patients with higher ovarian reserve needed lower dosages to reach the peak. Pre-trigger serum FSH levels of 15–20 mIU/ml were identified as beneficial for patients with robust ovarian reserve, and levels of 20–25 mIU/ml for those with low ovarian reserve. It was noted that the dosage and serum FSH levels optimized for blastocyst formation were lower than those required to maximize oocyte retrieval.

Conclusions: Gonadotropin dosage and serum FSH beyond a threshold offers limited benefit. Individualized stimulation strategies considering age, AMH, and serum FSH levels are recommended for optimizing outcomes.

Keywords: stimulated ovaries; egg retrieval; fertilization; embryo transfer; pregnancy; in vitro maturation (IVM)

Introduction

Ovarian stimulation during the in-vitro fertilization (IVF) cycle is a critical clinical process that directly affects the outcomes of IVF. It has been reported that the number of oocytes retrieved is positively associated with the live birth rate [1]. Essentially, increased ovarian stimulation through higher doses of gonadotropin administration results in a greater yield of oocytes. Nonetheless, when the yield exceeds 18 oocytes, the risk of ovarian hyperstimulation rises, necessitating a careful balance between the effectiveness of hyperstimulation and its associated risks [2]. Consequently, understanding the expected number of oocytes yielded with varying levels of stimulation is essential. The stimulation intensity is primarily associated with gonadotropins, particularly follicle-stimulating hormone (FSH). Therefore, the effective use of FSH preparations is a crucial skill for physicians in the reproductive field.

To achieve an optimal balance between a single dosage and the maximum daily dosages, 150 IU is generally recommended and recognized empirically as a standard dose. This dosage typically results in obtaining an ideal range of 8-14 oocytes for a significant portion of the ART patient population [3, 4]. However, with this dosage, a subset of patients with low or high ovarian reserve may show either a low or high response [5, 6]. Additionally, there has been recent debate regarding the optimal number of oocytes to retrieve. The optimal retrieval range of 8-14 oocytes is primarily derived from the standard Gonadotropin-Releasing Hormone (GnRH) agonist protocol with fresh embryo transfer (ET) cycles. Conversely, the combination of the GnRH antagonist protocol and the freeze-all strategy has gained popularity in many countries due to its enhanced safety profile. It has been well visited that the antagonist protocol and progestin-primed ovarian stimulation (PPOS) protocol, which involve GnRH agonist triggers for final oocyte maturation, serves a significant advantage in mitigating ovarian hyperstimulation

syndrome (OHSS) risk, particularly in younger patients with robust ovarian function [7-10]. Additionally, advances in cryopreservation technology have led to improve the frozen embryo transfer (FET), such that FET implantation and pregnancy rates now surpass those of fresh ET especially in patients with high ovarian reserve [11, 12]. It is well-established that the risk of OHSS can be significantly reduced through FET [12]. This key advantage has contributed to the widespread adoption of FET as a standard practice. For instance, in Japan, it has been reported that over 90% of embryo transfer cycles are currently conducted in FET cycles [13].

The improvement in safety has facilitated an increase in the number of oocytes collected. Additionally, trends indicate that the average age for commencing fertility treatment is rising in many countries [14]. This necessitates the retrieval of a higher number of oocytes, as it is well established that older patients require an increased quantity of oocytes to achieve a successful live birth. In fact, it is reported that patients with aged 38 or older has less than 50% of probability of having at least 1 child with 14 oocytes [10]. Similarly, it is reported that a higher number of oocytes retrieved improves the cumulative live birth rate (LBR) without impairing the primary transfer LBR, suggesting that ovarian stimulation strategies should aim to safely maximize the number of oocytes retrieved [15].

Considering these backgrounds, this study aims to retrospectively analyze the relationship between FSH dosage, serum FSH levels, and the number of oocytes retrieved, categorized by age and AMH levels as the most relevant factors influencing oocyte yield.

Materials And Methods

Patient population

This retrospective study comprised 53,764 IVF cycles conducted at our institution between January 2009 and April 2010. The inclusion criteria for this study followed those of a previously reported study [16], enrolling infertile couples seeking pregnancy through IVF. Exclusion criteria included cycles involving women aged 45 years or older, oocyte cryopreservation, or oocyte donation. Additionally, cycles with factors potentially influencing fertilization or blastocyst development, such as testicular sperm extraction (TESE) or in-vitro maturation (IVM), were excluded from the analysis. The cycles considered were categorized based on serum levels and female age groups, according to the method described by Shen et al. [17], classifying based on AMH and age. Specifically, subjects were divided into three groups according to AMH levels (AMH ≤ 1 ng/ml, 1 ng/ml < AMH ≤ 3 ng/ml, 3 ng/ml < AMH). Within each group, they were further subdivided by age into three categories (<35 years old, 35-40 years old, and 40-44 years old).

IVF Cycle Management

The stimulation protocols had no restriction, and the standard controlled ovarian hyperstimulation (COH) protocol was used. For oocyte stimulation, recombinant FSH or human menopausal gonadotropin (hMG) were employed. The total gonadotropin dose was determined by summing the doses of FSH and/or hMG administered during the ovarian stimulation period. Patients using follitropin delta were excluded from this study due to the difference in dose units (μg) compared to other products (IU).

To prevent premature LH surges, GnRH agonist, GnRH antagonist or oral progesterone were used. The final oocyte maturation trigger was administered when at least two follicles reached a diameter of 17-18 mm or when the attending physician determined the follicular cohort was mature. GnRHa was used as a final oocyte maturation trigger in cycles wherein GnRHa was not employed for ovulation suppression during COH, such as in GnRH antagonist protocols and progestin-primed ovarian stimulation protocols [18]. In cycles wherein GnRHa was utilized for ovulation suppression, such as in long or short agonist protocols, as well as in mild or antagonist cycle planning for fresh embryo transfer, hCG was primarily used. The dual trigger was applied when the initial oocyte retrieval yielded fewer mature oocytes than expected, indicating an inadequate response to the trigger.

Laboratory Intervention

After oocyte retrieval, IVF or intracytoplasmic sperm injection (ICSI) was conducted according to the semen analysis results and prior fertilization outcomes. The embryos were cultured to the cleavage or blastocyst stage and then either transferred or cryopreserved. Blastocysts were classified according to the Gardner's grading scale [19]. Those with grade 3BB or better on day 5 defined high-quality blastocysts. In calculating the blastocyst rate and the high-quality blastocyst rate, we excluded embryos undergoing cleavage-stage embryo transfer or freezing and used the number of embryos intended for blastocyst culture as the denominator.

Statistical Analysis

The primary outcomes measured was the total number of oocytes retrieved, and the secondary outcomes included the number of blastocysts. Scatter plots were utilized to identify trends for subsequent statistical analyses, specifically examining the relationship between gonadotropin dosage and the number of oocytes retrieved. The results were organized based on gonadotropin dose, with the average number of oocytes retrieved and the number of blastocysts per 100 cases were plotted to discern trends. Additionally, the data were stratified by total gonadotropin dose and analyzed for trends across varying dosage groups. Quadratic function approximation curves were displayed, and correlations within the scatter plots were assessed using the coefficient of determination (R^2). A similar analysis was conducted using serum FSH levels, where the serum FSH concentration represented the final value of the data within three days of the final maturation trigger. As in the analysis of gonadotropin dosage, the data were grouped by FSH value and correlated with a quadratic function. Welch's t-test was utilized to perform statistical analyses between groups for each category, with a p-value < 0.05 deemed to indicate statistical significance.

All statistical data were analyzed using Excel® (Microsoft 365) and EZR® (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing).

Ethical Considerations

This study is a retrospective cohort analysis, and no interventions were made regarding the IVF treatment process. The Institutional Review Board of Hanabusa Women's Clinic, which includes members selected by the institution and an external third-party institution, approved this study (approval number: 2025-05). Patients provided informed consent prior to the treatment period preceding IVF cycles, and separate confirmation for data analysis and publication via anonymization was obtained independently of treatment consent. Only patients who consented to provide their data were included in the database.

Results

Table 1 highlights the baseline characteristics of the study participants, categorized by age groups and serum AMH levels. The average age of the participants was 38.1 years, with a standard deviation of 4.4, while the mean AMH level was recorded at 2.1 ng/ml, accompanied by a standard deviation of 2.6. On average, participants underwent 3.9 ART attempts, including the current cycle, with basal FSH levels measured at 6.2 mIU/ml (SD: 7.3), increasing to 16.6 mIU/ml (SD: 7.7) following gonadotropin administration. The average duration of gonadotropin administration was 6.1 days (SD: 3.9) and total gonadotropin dose was 1,550 IU (SD: 1,350).

Figure 1 illustrates the relationship between the total gonadotropin dosage and the outcomes of oocyte retrieval and blastocyst formation. In all groups, the number of oocytes retrieved, and blastocysts formed demonstrated significant correlations with quadratic function approximation curves ($R^2 > 0.5$). This indicates that the oocyte retrieval count and blastocyst formation initially increase with gonadotropin dosage up to a certain level, beyond which they begin to decrease. Gonadotropin dosages positively influenced the number of oocytes retrieved, with optimal outcomes observed within the range of 2,500 to 4,000 IU. The approximation curves further demonstrate that younger individuals in each AMH category achieve higher peak oocyte retrieval counts with lower gonadotropin dosages compared to older age groups. The tables accompanying the figure detail the average number of oocytes retrieved, and blastocysts formed, categorized by gonadotropin dosage ranges, with the peak gonadotropin dosages highlighted in bold. In all groups, the gonadotropin dosage at which the number of oocytes retrieved peaks is higher than the dosage at which the number of blastocysts formed reaches its peak. Consequently, the optimal dose for maximizing the number of blastocysts observed ranged from 2,000 to 3,000 IU.

Table 2 provides an in-depth analysis of the correlation between gonadotropin dosage and IVF outcomes, with participants categorized based on AMH levels and age ranges. Among individuals with AMH levels below 1 ng/ml (N=23,324), the majority were aged between 40 and 45 years (N=14,334; 61.4%), while only 8.6% were under the age of 35 (N=1,997). This trend shifts with higher AMH levels; in the cohort with AMH levels exceeding 3 ng/ml (N=12,243), 47.2% of participants were under the age of 35 (N=5,773), 34.8% were aged 35 to 40 years (N=4,261), and 18.0% were aged between 40 and 45 years (N=2,209).

In all age groups, the data revealed that the retrieval of oocytes and formation of blastocysts declined once gonadotropin dosage surpassed a certain threshold. Notably, the gonadotropin dosage required to achieve the peak number of blastocysts and high-quality blastocysts was consistently lower than the dosage needed to maximize oocyte retrieval. This pattern became increasingly evident when analyzing blastocyst and high-quality blastocyst rates, where participants receiving gonadotropin doses exceeding 4,000 IU demonstrated the lowest rates of blastocyst formation and high-quality blastocyst production.

Similar analysis was conducted using serum FSH value instead of gonadotropin dosage. FSH values were recorded during the ovarian stimulation phase following gonadotropin administration. Similar to the observations in Figure 1, Figure 2 revealed that the number of retrieved oocytes and blastocysts reaches a peak at specific serum FSH values, after which a decline is observed. The number of oocytes retrieved was reached its peak at the serum FSH value was approximately 20 mIU/ml. In groups with higher AMH levels, the peak FSH concentration tended to be lower. Additionally, within the same AMH group, younger individuals achieved the maximum number of oocytes at lower FSH concentrations. Regarding the number of blastocysts, the peak FSH concentration decreased overall, showing a tendency to peak within the range of 15–20 mIU/ml. Particularly in the group under 35 years of age, the serum FSH concentration at peak was notably lower. Table 3 revealed the details of the results and indicates that, across most groups, the highest number of blastocysts and high-quality blastocysts were achieved at lower serum FSH values compared to those at the peak level where the highest number of oocytes were retrieved. When focusing on blastocyst formation rates and high-quality blastocyst rates, it was observed that in most groups, the highest rates occurred at an FSH level of 20 mIU/ml or below. The only exception was the group with AMH < 1 ng/ml and aged 40–45, where the highest blastocyst formation rates and high-quality blastocyst rates were observed at an FSH range of 25–30 mIU/ml.

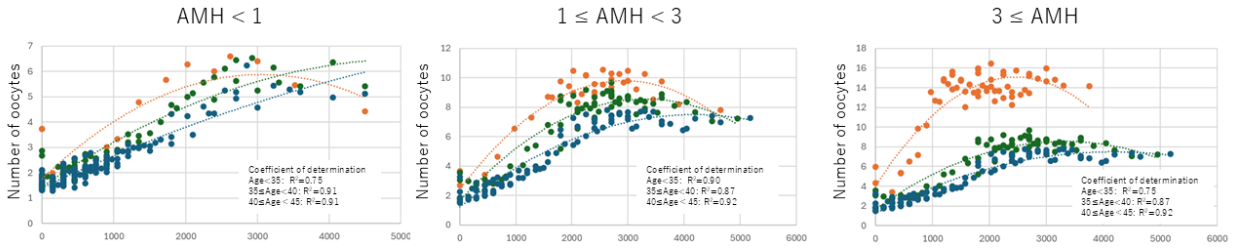
.	**Mean**	**SD**
age	38.1	4.4
AMH (ng/ml)	2.1	2.6
ART tempt	3.9	4.6
basal FSH (mIU/ml)	6.2	7.3
final FSH (mIU/ml)	16.6	7.7
Duration of stimulation (days)	6.1	3.9
Total gonadotropin dose (IU)	1550	1350

Table 1: Baseline characteristics of patients, duration of gonadotropin stimulation, and total administered dose of gonadotropins.

Total gonadotropin dose	**Number of cycles**	**Oocytes retrieved ± SD**	**Number of cycles culture to blastocyst stage**	**Number of blastocysts ± SD**	**High-quality blastocysts ± SD**	**Blastocyst formation rate (%)**	**High quality blastulation rate (%)**
AMH<1ng/ml (N=23,324)							
Age<35 (N=1,997)							
＜1000	1148	1.5 ± 0.1**	667	0.6 ± 0.0**	0.1 ± 0.0**	61.5	15.2
1000-2000	310	3.7 ± 3.0**	246	1.4 ± 1.4*	0.4 ± 0.7	63.1	19.0
2000-2500	169	5.7 ± 3.6	146	1.7 ± 2.4	0.4 ± 0.6	55.3	12.0
2500-3000	137	**5.9 ± 3.1**	124	1.9 ± 2.1	0.5 ± 0.8	60.0	15.8
3000-4000	163	5.9 ± 4.1	147	**1.9 ± 2.5**	**0.6 ± 0.9**	**64.1**	**20.2**
4000≤	70	4.8 ± 2.5**	66	1.1 ± 1.6**	0.2 ± 0.5**	51.0	6.7
35≤Age<40 (N=6,993)							
＜1000	4438	1.5 ± 1.3**	2770	0.5 ± 0.6**	0.1 ± 0.0**	56.6	11.7
1000-2000	1008	3.0 ± 2.1**	790	1.1 ± 1.4**	0.3 ± 0.7*	**60.0**	**16.7**
2000-2500	489	4.9 ± 3.1**	434	1.5 ± 1.6	**0.4 ± 0.6**	55.2	15.5

2500-3000	357	**5.6 ± 3.4**	310	**1.7 ± 1.5**	0.4 ± 0.8	54.5	11.8
3000-4000	482	5.5 ± 3.4	427	1.4 ± 1.7	0.3 ± 0.9**	51.8	9.3
4000≤	219	5.6 ± 3.2	208	1.4 ± 1.1	0.2 ± 0.5**	51.3	5.7
40≤Age<45 (N=14,334)							
＜1000	10964	1.3 ± 1.1**	6272	0.3 ± 0.5**	0.0 ± 0.2**	45.2	7.6
1000-2000	1882	2.5 ± 1.8**	1405	0.7 ± 0.9**	0.1 ± 0.4*	50.6	10.7
2000-2500	485	3.7 ± 2.5**	403	1.1 ± 1.3	0.2 ± 0.5	**52.0**	**11.4**
2500-3000	310	4.9 ± 3.2	264	**1.3 ± 1.4**	**0.3 ± 0.6**	47.4	10.2
3000-4000	451	**4.9 ± 3.1**	391	1.2 ± 1.3	0.2 ± 0.5*	46.0	7.5
4000≤	242	4.7 ± 2.9	213	1.0 ± 1.2*	0.1 ± 0.4**	40.9	4.0
1≤AMH<3 (N=18,197)							
Age<35 (N=3,738)							
＜1000	504	2.9 ± 0.1**	374	1.0 ± 0.0**	0.3 ± 0.0**	60.9	19.1
1000-2000	640	8.0 ± 4.7**	594	2.6 ± 2.3	0.8 ± 1.1	58.7	17.9
2000-2500	1046	9.0 ± 4.6*	983	**2.9 ± 3.2**	**0.9 ± 1.2**	**61.4**	**19.2**
2500-3000	718	**9.4 ± 4.7**	681	2.8 ± 3.4	0.8 ± 1.2*	58.0	15.3
3000-4000	701	9.4 ± 4.8	671	2.8 ± 3.3	0.6 ± 1.1**	57.7	13.5
4000≤	129	7.7 ± 3.8**	121	2.0 ± 2.8*	0.4 ± 0.7**	49.2	8.0
35≤Age<40 (N=6,485)							
＜1000	1134	2.5 ± 2.0**	836	0.8 ± 0.9**	0.2 ± 0.4**	57.4	13.8
1000-2000	970	5.8 ± 3.8**	842	1.9 ± 2.3**	0.5 ± 0.8*	**59.9**	16.7
2000-2500	1420	7.7 ± 4.2**	1336	2.4 ± 2.3	**0.7 ± 1.1**	58.1	**16.0**
2500-3000	1141	**8.3 ± 4.6**	1066	**2.4 ± 2.3**	0.6 ± 0.9	55.4	13.0
3000-4000	1419	8.1 ± 4.5	1328	2.2 ± 2.4*	0.5 ± 0.9*	53.4	11.7
4000≤	401	7.3 ± 4.0**	376	1.8 ± 1.8**	0.4 ± 0.7**	49.7	8.6
40≤Age<45 (N=7,974)							
＜1000	3057	2.0 ± 1.6	2195	0.4 ± 0.7**	0.1 ± 0.2**	46.1	7.0
1000-2000	1384	4.1 ± 2.9	1212	1.1 ± 1.3**	0.2 ± 0.5*	50.3	10.7
2000-2500	1024	6.4 ± 3.7	960	**1.9 ± 1.8**	**0.4 ± 0.8**	**53.2**	**11.9**
2500-3000	778	**7.1 ± 4.0**	732	1.9 ± 1.7	0.3 ± 0.7*	49.5	9.1
3000-4000	1198	**7.1 ± 4.1**	1140	1.7 ± 1.7*	0.3 ± 0.6*	46.4	7.6
4000≤	533	6.8 ± 3.9	501	1.4 ± 1.5**	0.2 ± 0.5**	43.4	4.0
3≤AMH (N=12,243)							
Age<35 (N=3,738)							
＜1000	904	5.9 ± 0.2**	742	2.0 ± 0.1**	0.6 ± 0.0**	61.4	**18.7**
1000-2000	2309	13.6 ± 7.3	2199	4.2 ± 3.6	1.3 ± 1.8	60.7	18.5
2000-2500	1457	13.6 ± 7.1	1391	**4.3 ± 4.8**	**1.3 ± 1.7**	**61.3**	18.3
2500-3000	625	13.7 ± 6.7	594	4.2 ± 4.6	1.2 ± 1.6	58.8	17.0
3000-4000	427	**14.3 ± 6.7**	410	3.9 ± 4.9	1.0 ± 1.5*	55.6	13.6
4000≤	51	13.2 ± 8.7	46	3.7 ± 5.3	0.9 ± 1.1*	51.2	11.1
35≤Age<40 (N=4,261)							
＜1000	560	4.5 ± 4.2**	448	1.4 ± 1.8**	0.3 ± 0.7**	58.0	14.5
1000-2000	1133	12.2 ± 7.1	1067	3.7 ± 3.6	1.0 ± 1.5	**59.1**	**16.4**
2000-2500	1193	**12.5 ± 6.7**	1127	**3.8 ± 3.5**	**1.1 ± 1.4**	58.5	16.3
2500-3000	712	12.4 ± 6.0	677	3.6 ± 3.3	0.8 ± 1.2**	57.3	13.4
3000-4000	584	11.8 ± 6.3	565	3.2 ± 3.6	0.7 ± 1.1**	53.3	12.0
4000≤	79	10.2 ± 5.4**	74	2.5 ± 2.7**	0.5 ± 1.0**	49.1	8.1
40≤Age<45 (N=2,209)							
＜1000	444	2.8 ± 2.7**	319	0.7 ± 1.2**	0.1 ± 0.4**	50.5	9.0
1000-2000	422	7.5 ± 5.3**	389	2.0 ± 2.3**	0.5 ± 1.0	48.8	**12.9**
2000-2500	430	10.3 ± 5.6	416	**2.8 ± 2.3**	**0.6 ± 0.9**	**51.6**	10.5
2500-3000	348	**10.5 ± 6.0**	334	2.7 ± 2.3	0.5 ± 0.9	49.8	9.9
3000-4000	431	10.4 ± 5.5	420	2.5 ± 2.2	0.5 ± 0.9	45.7	9.4
4000≤	134	9.8 ± 4.7	129	2.0 ± 1.8**	0.3 ± 0.7**	42.5	5.2

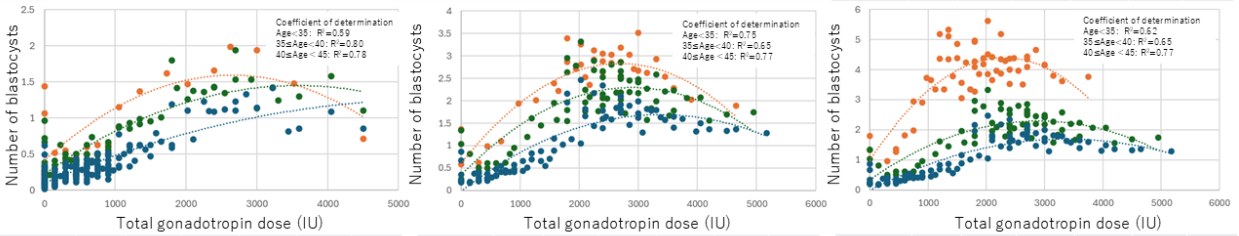
Table 2: The correlation between gonadotropin dosage and IVF outcomes was analyzed, categorized by AMH levels and age categories. Bold indicates the highest values among respective groups, based on comparative figures before rounding to one decimal place. High-quality blastocysts were defined according to Gardner's grading scale as 3BB or higher on day 5. An asterisk (*) indicates a statistically significant difference with a p-value of less than 0.05 when compared to the group indicated in bold, while a double asterisk (**) signifies a p-value of less than 0.01. The p-values were calculated using Welch's t-test.



Total dose (IU)	<1000	1000-2000	2000-2500	2500-3000	3000-4000	4000≤
Age<35	1.5	3.7	5.7	5.8	**5.9**	4.8
35≤Age<40	1.5	3.0	4.9	**5.6**	5.5	5.6
40≤Age<45	1.3	2.5	3.7	4.8	**4.9**	4.7

Total dose (IU)	<1000	1000-2000	2000-2500	2500-3000	3000-4000	4000≤
Age<35	2.9	8.0	9.0	9.3	**9.4**	7.7
35≤Age<40	2.5	5.8	7.7	**8.3**	8.1	7.3
40≤Age<45	2.0	4.1	6.4	7.0	**7.1**	6.8

Total dose (IU)	<1000	1000-2000	2000-2500	2500-3000	3000-4000	4000≤
Age<35	5.9	13.6	13.6	13.7	**14.3**	13.2
35≤Age<40	4.5	12.2	**12.5**	12.4	11.8	10.2
40≤Age<45	2.8	7.5	10.3	**10.5**	10.4	9.8

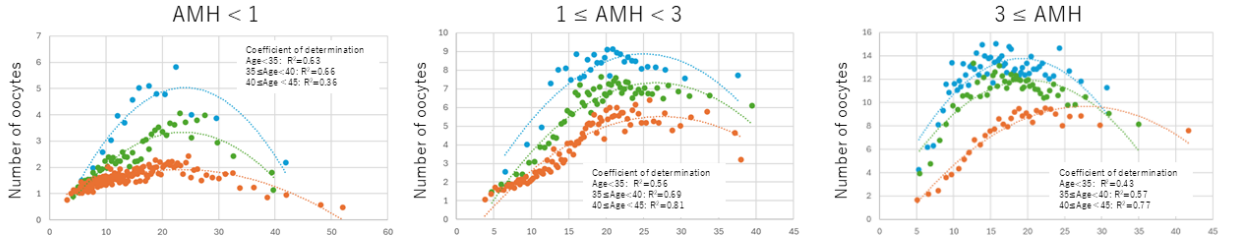


Total dose (IU)	<1000	1000-2000	2000-2500	2500-3000	3000-4000	4000≤
Age<35	0.6	1.4	1.7	**1.9**	1.8	1.1
35≤Age<40	0.5	1.1	1.5	**1.7**	1.4	1.4
40≤Age<45	0.3	0.7	1.1	**1.3**	1.2	1.0

Total dose (IU)	<1000	1000-2000	2000-2500	2500-3000	3000-4000	4000≤
Age<35	1.0	2.6	**2.9**	2.8	2.8	2.0
35≤Age<40	0.8	1.9	**2.4**	**2.4**	2.2	1.8
40≤Age<45	0.4	1.1	**1.9**	**1.9**	1.7	1.4

Total dose (IU)	<1000	1000-2000	2000-2500	2500-3000	3000-4000	4000≤
Age<35	3.0	**4.1**	4.0	3.8	3.3	3.1
35≤Age<40	1.8	3.3	**3.6**	3.1	2.8	2.3
40≤Age<45	0.8	1.8	2.2	**2.3**	2.0	1.8

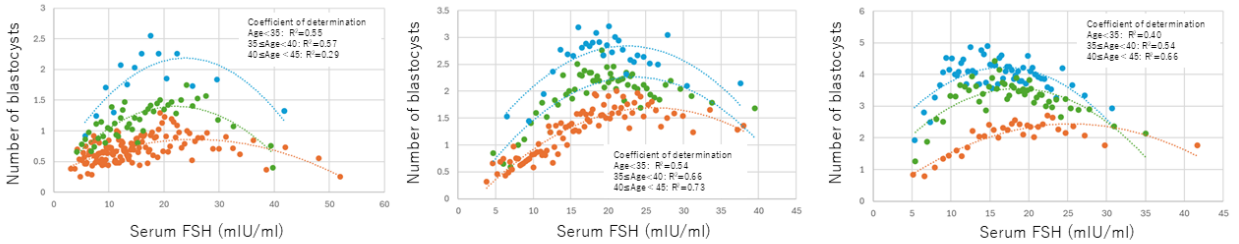
Figure 1: Scatter plots illustrating the correlation between total gonadotropin dose and number of oocytes retrieved and blastocysts, categorized by AMH levels and age groups. The data are organized according to gonadotropin dosage, with the average number of oocytes retrieved and blastocysts per 100 cases plotted to identify trends. The scatter plot includes approximated curves described by quadratic functions, with correlations represented by determination coefficients. Orange points indicate individuals under 35 years of age, green points represent those aged 35 ≤ Age < 40, and blue points correspond to those aged 40 ≤ Age < 45. Across all groups, oocyte retrieval reached its peak at certain gonadotropin dosages, followed by a decline. The table beneath the figure presents the mean numbers of oocytes retrieved and blastocysts formed, grouped by age and gonadotropin dosage. Bold values highlight peaks within each group.



FSH	<10	10-15	15-20	20-25	25-30	30≤
Age<35	2.0	3.5	4.9	**5.1**	4.0	2.5
35≤Age<40	1.6	2.3	2.8	**3.5**	**3.5**	2.1
40≤Age<45	1.3	1.7	1.9	**2.2**	1.8	1.3

FSH	<10	10-15	15-20	20-25	25-30	30≤
Age<35	3.1	6.9	8.2	**8.6**	8.0	7.6
35≤Age<40	2.1	4.4	6.5	**7.0**	6.8	6.6
40≤Age<45	1.8	3.0	4.8	**5.7**	5.4	5.1

FSH	<10	10-15	15-20	20-25	25-30	30≤
Age<35	8.6	12.8	**13.2**	13.0	12.1	11.4
35≤Age<40	6.3	11.0	**12.0**	11.0	10.0	8.5
40≤Age<45	2.9	6.5	8.8	**9.2**	8.7	7.8



FSH	<10	10-15	15-20	20-25	25-30	30≤
Age<35	0.9	1.4	**2.0**	1.7	1.5	1.1
35≤Age<40	0.6	0.8	1.0	**1.2**	**1.2**	0.7
40≤Age<45	0.3	0.4	0.5	**0.7**	0.6	0.4

FSH	<10	10-15	15-20	20-25	25-30	30≤
Age<35	1.1	2.1	**2.8**	2.6	2.6	2.0
35≤Age<40	0.6	1.5	**2.1**	2.0	1.9	1.7
40≤Age<45	0.4	0.7	1.4	**1.5**	1.4	1.3

FSH	<10	10-15	15-20	20-25	25-30	30≤
Age<35	3.0	**4.1**	4.0	3.8	3.3	3.1
35≤Age<40	1.8	3.3	**3.6**	3.1	2.8	2.3
40≤Age<45	0.8	1.8	2.2	**2.3**	2.0	1.8

Figure 2: Scatter plots analyzing the number of oocytes retrieved and blastocysts formed, classified according to AMH levels and age groups. The data are structured based on serum FSH values, recorded during the ovarian stimulation phase within three days of the final maturation trigger. Blue points indicate individuals under 35 years of age, green points represent those aged 35 ≤ Age < 40, and orange points correspond to those aged 40 ≤ Age < 45. The table beneath the figure presents the mean numbers of oocytes retrieved and blastocysts formed, grouped by age and gonadotropin dosage. Bold values highlight peaks within each group.

Serum FSH value (mIU/ml)	Number of cycles	Oocytes retrieved ± SD	Number of cycles culture to blastocyst stage	Number of blastocysts ± SD	High-quality blastocysts ± SD	Blastocyst formation rate (%)	High quality blastulation rate (%)
AMH<1ng/ml (N=16,187)							
Age<35 (N=1,465)							
＜10	282	2.0 ± 0.1**	667	0.9 ± 0.0**	0.2 ± 0.0**	**69.0**	19.2
10-15	383	3.5 ± 4.6**	246	1.4 ± 1.7**	0.4 ± 0.7**	63.5	16.7
15-20	349	4.9 ± 5.8	146	**2.0 ± 3.5**	**0.6 ± 1.1**	64.2	**19.8**
20-25	223	**5.1 ± 4.9**	124	1.7 ± 2.0	0.5 ± 0.9	56.8	17.8
25-30	117	4.0 ± 4.4*	147	1.5 ± 2.8	0.4 ± 0.8	59.8	16.9
30≤	111	2.5 ± 3.4**	66	1.1 ± 2.2**	0.3 ± 0.5**	52.5	10.4
35≤Age<40 (N=4,541)							
＜10	1192	1.6 ± 1.8**	2770	0.6 ± 0.7**	0.1 ± 0.3**	58.5	11.0
10-15	1211	2.3 ± 2.6**	790	0.8 ± 1.1**	0.2 ± 0.4**	**59.0**	**14.0**
15-20	942	2.8 ± 3.1**	434	1.0 ± 1.2	**0.3 ± 0.5**	55.1	**14.0**
20-25	581	**3.5 ± 3.7**	310	**1.2 ± 1.4**	0.3 ± 0.6	54.9	12.7
25-30	330	3.5 ± 3.6	427	1.2 ± 1.5	0.3 ± 0.6	52.4	12.2
30≤	285	2.1 ± 2.7**	208	0.7 ± 0.8**	0.1 ± 0.2**	43.5	4.8
40≤Age<45 (N=10,181)							
＜10	3260	1.3 ± 1.1**	6272	0.3 ± 0.7**	0.0 ± 0.2**	45.9	7.2
10-15	2913	1.7 ± 1.5**	1405	0.4 ± 1.1**	0.1 ± 0.2**	44.9	9.0
15-20	1852	1.9 ± 2.0**	403	0.5 ± 1.2	0.1 ± 0.2**	44.7	8.1
20-25	1058	**2.2 ± 2.6**	264	**0.7 ± 1.4**	**0.1 ± 0.3**	45.6	7.5
25-30	496	1.8 ± 2.1**	391	0.6 ± 1.5	0.1 ± 0.3	**46.1**	**10.9**
30≤	602	1.3 ± 1.8**	213	0.4 ± 0.8*	0.0 ± 0.1**	43.3	2.7
1≤AMH<3 (N=16,430)							
Age<35 (N=3,060)							
＜10	167	3.1 ± 0.1**	374	1.1 ± 0.0**	0.4 ± 0.0**	61.5	**20.8**
10-15	431	6.9 ± 5.5**	594	2.1 ± 2.0**	0.6 ± 1.0**	57.8	17.4
15-20	1007	8.2 ± 4.8*	983	**2.8 ± 3.2**	**0.9 ± 1.3**	**63.1**	20.2
20-25	979	**8.6 ± 4.5**	681	2.6 ± 2.9	0.7 ± 1.1	58.7	16.4
25-30	342	8.0 ± 4.5*	671	2.6 ± 3.3	0.7 ± 1.1	61.9	17.1
30≤	134	7.6 ± 4.1**	121	2.0 ± 2.6**	0.3 ± 0.6**	51.7	7.4
35≤Age<40 (N=5,889)							
＜10	578	2.1 ± 2.1**	836	0.6 ± 0.9**	0.2 ± 0.4**	52.9	14.5
10-15	909	4.4 ± 3.7**	842	1.5 ± 1.7**	0.4 ± 0.8**	**58.5**	**17.2**
15-20	1737	6.5 ± 4.2**	1336	**2.1 ± 2.0**	**0.6 ± 1.0**	58.3	16.0
20-25	1687	**7.0 ± 4.1**	1066	2.0 ± 1.8	0.5 ± 0.9**	55.5	14.1
25-30	671	6.8 ± 4.1	1328	1.9 ± 1.8**	0.4 ± 0.8**	52.6	12.2
30≤	307	6.6 ± 4.2**	376	1.7 ± 1.7**	0.3 ± 0.6**	51.3	7.0
40≤Age<45 (N=7,481)							
＜10	3057	1.8 ± 1.5**	2195	0.4 ± 0.9**	0.1 ± 0.2**	46.1	7.0
10-15	1384	3.0 ± 2.5**	1212	0.7 ± 1.7**	0.1 ± 0.4*	50.3	10.7
15-20	1024	4.8 ± 3.7**	960	1.4 ± 2.0*	0.3 ± 0.6	**53.2**	**11.9**
20-25	778	**5.7 ± 3.9**	732	**1.5 ± 1.8**	**0.3 ± 0.7**	49.5	9.1
25-30	1198	5.4 ± 3.6	1140	1.5 ± 1.8	0.2 ± 0.5*	46.4	7.6
30≤	533	5.1 ± 3.7*	501	1.3 ± 1.7**	0.2 ± 0.5**	43.4	4.0
3≤AMH (N=13,432)							
Age<35 (N=5,784)							
＜10	904	8.6 ± 0.3**	742	3.0 ± 0.1**	1.0 ± 0.1**	**61.4**	**18.7**
10-15	2309	12.8 ± 7.5	2199	**4.1 ± 3.6**	**1.3 ± 1.8**	60.7	18.5
15-20	1457	**13.2 ± 6.9**	1391	4.0 ± 4.7	1.2 ± 1.7	61.3	18.3
20-25	625	13.0 ± 6.6	594	3.8 ± 4.0*	1.1 ± 1.6	58.8	17.0
25-30	427	12.1 ± 6.2*	410	3.3 ± 4.0**	1.1 ± 1.7	55.6	13.6
30≤	51	11.4 ± 6.7*	46	3.1 ± 4.2*	0.7 ± 1.3**	51.2	11.1
35≤Age<40 (N=4,714)							
＜10	560	6.3 ± 6.3**	448	1.8 ± 2.2**	0.5 ± 1.0**	58.0	14.5
10-15	1133	11.0 ± 7.2**	1067	3.3 ± 3.1	0.9 ± 1.5	**59.1**	**16.4**
15-20	1193	**12.0 ± 6.6**	1127	**3.6 ± 3.0**	**1.0 ± 1.3**	58.5	16.3
20-25	712	11.0 ± 6.0**	677	3.1 ± 2.6**	0.8 ± 1.2*	57.3	13.4
25-30	584	10.0 ± 5.3**	565	2.8 ± 2.3**	0.6 ± 1.0**	53.3	12.0

30≤	79	8.5 ± 4.2**	74	2.3 ± 1.7**	0.5 ± 0.8**	49.1	8.1
40≤Age<45 (N=2,934)							
＜10	444	2.9 ± 2.9**	319	0.8 ± 2.2**	0.1 ± 0.5**	50.5	9.0
10-15	422	6.5 ± 5.7**	389	1.8 ± 3.1**	0.5 ± 0.9	48.8	**12.9**
15-20	430	8.8 ± 5.6	416	2.2 ± 3.0	0.5 ± 0.9	**51.6**	10.5
20-25	348	**9.2 ± 5.1**	334	**2.3 ± 2.6**	**0.5 ± 0.9**	49.8	9.9
25-30	431	8.7 ± 4.4	420	2.0 ± 2.3	0.4 ± 0.8*	45.7	9.4
30≤	134	7.8 ± 4.5**	129	1.8 ± 1.7*	0.2 ± 0.6**	42.5	5.2

Table 3: The correlation between serum FSH after gonadotropin administration and IVF outcomes, segmented by AMH levels and age groups. This analysis includes cases where serum FSH was measured within three days of the final maturation trigger. Bold indicates the highest values among respective groups, based on comparative figures before rounding to one decimal place. An asterisk (*) indicates a statistically significant difference with a p-value of less than 0.05 when compared to the group indicated in bold, while a double asterisk (**) signifies a p-value of less than 0.01. The p-values were calculated using Welch's t-test.

Discussion

The number of oocytes retrieved is one of the critical factors contributing to the success of IVF, and numerous studies have reported that an increase in the number of oocytes retrieved is associated with higher pregnancy rates [1]. Various factors influence the number of oocytes retrieved, with the most significant being the patient's age and ovarian reserve, as indicated by their AMH levels. In addition to these patient-specific characteristics, the dosage

of gonadotropins plays a pivotal role, since gonadotropins facilitate the growth and development of multiple follicles by bypassing the limitations of natural physiological processes [20]. Our study showed that up to certain thresholds, the dosage of gonadotropin and serum FSH levels were positively correlated with an increase in the number of oocytes retrieved and blastocysts. However, this correlation declined after reaching peak values. Several researchers have reported similar findings. Clark et al. observed a negative correlation between gonadotropin dosage and the number of oocytes retrieved [21]. Zielinski et al. noted that for patients predicted to produce 4–8 mature oocytes (MII), an increase in gonadotropin dosage resulted in a decline in oocyte count. Conversely, patients with low [1–3] and high [9–12] MII predictions achieved optimal results when administered a daily dose of 225 IU [22]. These observations suggest that appropriate gonadotropin doses vary among individuals based on ovarian reserve.

The variability in appropriate doses of gonadotropin among individuals is attributed to a range of factors. In addition to above mentioned AMH value, age and body weight are also considered important factors. In this study, it was observed that the total gonadotropin dose necessary to optimize the number of blastocysts is lower in younger cohorts compared to patients aged 40 or older with equivalent AMH levels. Similarly, Leijdekkers et al. reported that female age and body weight modified the effect of individualized FSH dosing [23]. It has been suggested that female age and body weight contribute to such heterogeneity. The ovarian reserve quantitatively and qualitatively diminishes with advancing age [24], and serum FSH levels appear to have an inverse association with body weight [25]. Based on these facts, fixed daily dose determined by an algorithm based on patient's AMH and weight are used in follitropin delta [26, 27]. In addition, recent study reported the dose adjustment by starting dose calculator based on age and AMH showed significant concordance rate between predicted and actual number of oocytes [28]. These efforts will assist in determining the suitable initial dose for most patients. However, there remain ongoing concerns regarding a subset of patients who fail to achieve the expected number of oocytes in clinical practice. This discrepancy may be attributed to fluctuations in FSH activity between different product batches and variations in individual FSH metabolism. Alviggi et al. reported that a higher FSH consumption is expected in homozygotes for the A allele of the FSHR (rs1394205) polymorphism than carriers of the G allele [29]. The evidence suggests that determining the appropriate gonadotropin dose can be challenging in certain cases and may require adjustment following administration.

In order to adjust individual differences in the optimal dosage of gonadotropins, serum FSH concentration, is considered a useful reference for determining the appropriate gonadotropin dosage. In this study, the number of oocytes retrieved reached its peak at the serum FSH value was approximately 20 mIU/ml. However, when focusing on blastocyst formation rates and high-quality blastocyst rates, it was observed that in most groups, the highest rates occurred at an FSH value of below 20 mIU/ml. It is clear that the number of blastocysts is more directly associated with successful pregnancy outcomes compared to the number of oocytes retrieved. Consequently, it is considered optimal to establish the target serum FSH concentration within the range of 15–20 mIU/ml, as this interval consistently corresponds to the highest blastocyst yield across most groups. Similar findings have also been reported by Arce et al., who demonstrated that although increasing the dosage of FSH preparations results in a higher number of oocytes retrieved, the contribution to the number of blastocysts and pregnancy rates is limited. This aligns with the results of the present study and provides an important perspective when determining the appropriate dose of ovulation induction agents [30].

The important point of the study is FSH above threshold resulted in the decrease in the number of oocytes retrieved. Moreover, the dosage and serum FSH levels optimized for blastocyst formation were lower than those required to maximize oocyte retrieval. These facts indicate that excessive FSH may have the detrimental effect on oocytes. A possible explanation is the altered expression of FSH receptor. It is reported that continuous exposure to high concentrations of FSH result in decreased FSHR expression, leading to reduced ovarian response [31]. Furthermore, Clark et al. stated that an analysis of transcription profiles in granulosa cells, cumulus cells, and oocytes demonstrated that the excessive administration of FSH resulted in deviations from normal gene expression patterns to abnormal patterns with increasing severity of follicular abnormality with the excessive dose [32]. Premature luteinization is another potential mechanism that has been documented in women following the administration of high doses of FSH during ovarian stimulation, resulting in significant disruptions to the follicular microenvironment [33]. This phenomenon is reported to be induced by the stimulatory effect of exogenous FSH on the expression of other enzymes required for estrogen synthesis. It stimulates 3β-HSD (3β-hydroxysteroid dehydrogenase) expression and progesterone biosynthesis in human granulosa cells and ovarian tissue samples, thus leading to an increase in the conversion of pregnenolone to progesterone [34]. High concentrations of serum progesterone have been shown to inhibit the proliferation of granulosa cells, thereby reducing the growth rate of follicles. This suggests that progesterone produced with excessive FSH decreases the oocyte yields [35]. In fact, bovine studies demonstrated that superovulation with high FSH doses did not increase the number of ovulatory sized follicles produced and

decreased ovulation rate relative to lower doses [36]. Regarding oocyte quality, Bernstein et al. introduced the "FSH OOToxicity Hypothesis," suggesting that elevated FSH levels may result in chromosomal abnormalities and spindle misalignment, thereby potentially reducing oocyte quality [37]. Similarly, Dursun et al. indicated that FSH might impair cytoskeletal dynamics and decrease the accuracy of meiosis [38]. Combelles et al. also observed that excessive FSH signaling may lead to the degeneration of transzonal projections (TZPs), possibly hindering communication between oocytes and surrounding cells [39]. These reports indicate that excessive FSH deteriorate the oocyte quality and support the findings of our present study.

The main limitation of this study is its retrospective design, causing variations in ovarian responses within the same AMH and age groups. Therefore, selection bias may exist between groups with similar AMH levels when determining the appropriate FSH dosage. Thus, prospective studies are needed to accurately determine gonadotropin dosage based on different patient backgrounds.

Furthermore, this study encompassed both urinary HMG and recombinant FSH, which might exhibit variations in FSH activity despite identical gonadotropin dosages. Consequently, future research under a uniform gonadotropin product may be advisable. Nonetheless, our investigation not only considered the gonadotropin dosage but also measured serum FSH levels. Therefore, this limitation has been addressed. Finally, given that this study was conducted at a single institution with 99% of participants being Asian, predominantly Japanese, generalizing the findings to patient populations of other racial backgrounds may be difficult.

Conclusions

Gonadotropin dosage and serum FSH beyond a threshold offers limited benefit and the dosage and serum FSH levels optimized for blastocyst formation were lower than those required to maximize oocyte retrieval. Individualized stimulation strategies considering age, AMH, and serum FSH levels are recommended for optimizing outcomes.

Disclosures

Conflict of interest: Noritoshi Enatsu, Yihsien Enatsu, Kunihiro Enatsu, Ai Yamada, Yuri Mizusawa, Eri Okamoto, Shoji Kokeguchi, Hiroaki Sibahara and Masahide Shiotani declare that they have no conflict of interest.

Human rights statement and informed consent: All patients were well informed and written informed consent was obtained prior to the treatment period.

Animal rights: This article does not contain any studies with animal subjects performed by the any of the authors.

The statement of approval from Institutional Review Board: All procedures in this study were in accordance with the ethical standards of the Ethical Committee in accordance with the ethical principles that have their origin in the Declaration of Helsinki 1964 and its later amendments. This study was approved by Ethical Committee of Hanabusa Women's Clinic consists of members chosen by our institute and third-party medical institute (approval number; 2025-05).

Declaration of generative AI and AI-assisted technologies in the writing process: During the preparation of this work, the author utilized Microsoft Copilot (GPT-4.5) to enhance the readability of the English text. Following the use of this tool, the author meticulously reviewed and edited the content as necessary, assuming full responsibility for the final publication.

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