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Analysis of Treatment Outcomes of Infertile Japanese Women Based on Serum Anti-Müllerian Hormone Levels to Investigate Its Criteria in Infertile Practice

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Abstract

We analyzed the clinical data of infertility treatment performed with reference to serum anti-Müllerian hormone (AMH) levels. Through this analysis, we studied the clinical criteria of serum AMH levels as a treatment strategy.

From 2014 to 2018, 495 infertile patients were enrolled in the present study, and clinical data were collected until the end of 2020. Patients were divided into three groups according to serum AMH levels: group A (n=123), a low group (AMH<1.35 ng/mL); group B (n=248), a middle group ($1.35 \le AMH \le 5.19 \text{ ng/mL}$); and group C (n=124), a high group (AMH $\ge 5.19 \text{ ng/mL}$). The patient characteristics, results of infertility therapy, and obstetric outcomes were compared among the groups.

Age was significantly different among the three groups. The pregnancy rate was lowest in group A, where pregnant patients were younger and had higher AMH levels. The cumulative birth rates were higher in younger women in groups A and B; however, the rates did not differ regarding serum AMH levels in both groups. Age did not affect the cumulative birth rates in group C. There was no relationship between serum AMH levels and the occurrence of complications during pregnancy. The present study was of value in examining the criteria of serum AMH levels in determining the treatment plan in Japanese fertility practice.

Keywords: Anti-Müllerian hormone; Infertility; Japanese; Live birth; Pregnancy

Introduction

Recently, anti-Müllerian hormone (AMH) has become one of the most important serum markers for determining treatment strategies for infertility. There are many reports on AMH use in determining the starting dose of follicle stimulating hormone (FSH) during in vitro fertilization (IVF) and in predicting the number of eggs that can be retrieved [1-3]. Serum AMH value is also attracting attention as a preventive measure against ovarian hyperstimulation syndrome (OHSS) and as a diagnostic aid in cases of polycystic ovary syndrome (PCOS) [4-6]. The number of developing follicles is low in cases of low serum AMH levels [7,8]. A diagnostic criterion for serum AMH level is proposed as a poor ovarian response (POR) in the Bologna consensus [9].

In response to these reports, we employed AMH as a decision marker for planning a treatment strategy since 2014, instead of early follicular serum FSH levels [10]. However, there are no reports analyzing infertility practices according to serum AMH levels in Japan, where the environment of fertility practice is different from that in Western countries, and we do not have diagnostic criteria for serum AMH levels to be low or high.

In this study, we divided our patients into three groups according to the first and third quartiles of serum AMH levels and analyzed the results of infertility practice. Through this analysis, we studied the serum AMH criteria in determining the reatment

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plan. Moreover, we analyzed the perinatal outcomes. Many studies have reported high serum AMH levels in PCOS, which is a metabolic syndrome with insulin resistance [11,12]. We examined serum AMH levels as a pre-conception marker for gestational diabetes mellitus (GDM).

Materials and Methods

Patients and therapies: This is a single-center retrospective cohort study with a regimented treatment for infertile couples. The study design was approved by the appropriate Ethics Committee of the Yamaguchi Prefectural Grand Medical Center. From January 2014 to December 2018, 512 infertile women visited our hospital and underwent blood sampling for AMH measurement on early follicular days (between the 3rd and 5th days). The serum AMH concentration was assayed by SRL Co. Japan (ELISA: 2014.1 ~ 2016.6, CLEIA: 2016.7 ~ 2018.4, ECLIA: 2018.4 ~ 12). Serum AMH values were adjusted in the CLEIA assay system using the correlation coefficients before analysis. Seventeen participants with serum AMH levels below the lower sensitivity of each assay system were excluded, and data from 495 infertile patients were finally analyzed in the present study.

After screening examinations, patients with ovulatory disturbance or unknown factors received step-up treatments in natural, clomiphene citrate, and gonadotropin injection cycles with or without intrauterine insemination (IUI). Each treatment cycle was repeated 3 to 5 times. The other patients with severe male factor and/or uterine, tubal, or ovarian factors first received appropriate therapy according to each disease, similarly followed by step-up treatments. When these therapies were not effective, IVF was finally performed. When immediate IVF was appropriate in some cases, they underwent IVF instead of step-up treatments. Clomiphene citrate was prescribed 50-150 mg/day from the 5th to 9th days of menstrual cycles, and the injection dose of gonadotropin was 75-150 IU/day for the first gonadotropin treatment therapy. For IVF, the initial dose was determined based on the results of gonadotropin treatment therapy. Those starting drug doses of each treatment cycle were decided by Y.N. Pregnancy data were collected until the end of 2020. Pregnancy was diagnosed by confirmation of the gestational sac. When they succeeded in obtaining a couple of pregnancies during these days, the first conceived data were

assessed. When patients succeeded in giving birth until the end of 2020 after miscarriage during the first pregnancy, those numbers were counted as the cumulative births.

Patients were divided into three groups according to their serum AMH levels: group A, AMH $<25^{th}$ percentile (n=123); group B, 25th percentile \leq AMH $<75^{th}$ percentile(n=248); and group C, 75thpercentile \leq AMH (n=124). The results in clinical practice were compared among the three groups: age, infertility factors, therapy to conceive, pregnancy rates, abortion rates, and cumulative birth rates. Age and serum AMH levels were subsequently compared between pregnant and non-pregnant women in each group. The obstetric outcomes in singleton pregnancies managed in our hospital were compared with data from the Japan Society of Obstetrics and Gynecology (JSOG) [13].

Statistical analysis: Data on age, AMH, and body mass index (BMI) were presented as a median level with minimum-maximum values. The data were analyzed with Kruskal-Wallis and Mann-Whitney U tests with Bonferroni correction for the comparison of three groups and Mann-Whitney U test for two groups comparison. Chi-square test was used in the 3×2 table analysis for the other data. Differences were considered significant at p<0.05.

Results

The present study analyzed the data of 495 infertile women (315 primary infertility and 180 secondary infertility) with serum AMH levels (median: 2.72 ng/mL, 0.02 -68.3 [minimummaximum]), ages (35 years, 21-45), and BMI (20.7 Kg/m², 15.8-36.9). The 25th percentile and 75th percentile of serum AMH levels were 1.35 and 5.19 ng/mL, respectively, and the median AMH levels in groups A, B, and C were 0.64, 2.72, and 8.09 ng/mL, respectively. The median age of patients in each group was significantly different (Table 1). The uterine factors were significantly higher in group A than those in the other two groups. The rates of tubal factors and unknown causes were significantly lower, and the rate of PCOS diagnosed by the JSOG criteria (Table 2) was significantly higher in group C compared with those in the other two groups (Table 1). The rates of other infertility causes, such as ovulatory disorders, endometriosis, and male factors, were not different among the three groups.

-	Group A	Group B	Group C		
Number of patients	123	248	124		
AMH (ng/mL) [†]	0.64 (0.02-1.34)	2.72 (1.35-5.18)	8.09 (5.19-68.3)		
Age (years) [†]	38 (27-45)*	35 (21-45)*	32 (22-42)*		
BMI (Kg/m²) [†]	21.1 (16.9-34.9)	20.6 (15.8-36.9)	20.3 (15.8-36.9)		
Number of primary sterility	70 (56.9%)	162 (65.3%)	83 (66.9%)		
Infertility causes [‡]					
Uterine factors	31 (21.8%)**	37 (13.2%)	11 (7.2%)		
Tubal factors	15 (10.6%)	31 (11.0%)	5 (3.3%)***		
PCOS	0	7 (2.5%)	43 (28.3%)****		
Unknown	Unknown 39 (27.5%) 64 (22.8%) 14 (9		14 (9.2%)***		
Note: [†] : Data of AMH, age and BMI are median (minimum-maximum).					
*: Some patients have a couple of causes. The presenting causes were significant ones.					
*: p<0.0000 vs the other two groups by Mann-Whitney U test with Bonferroni correction.					
**: p<0.05 vs the other groups by Chi-square test.					
***: p<0.05 vs the other groups by Chi-square test.					
****: p<0.0000 vs the other groups by Chi-square test.					

 Table 1: Clinical characteristics in the three groups.

PCOS meets all of the following three criteria.

1. Abnormal menstruation

2. Polycystic ovaries

3. High serum androgen levels and/or high basal serum LH and normal FSH levels

Note: 1. indicates amenorrhea, oligomenorrhea and anovulatory cycle.

2. indicates more than 10 follicles in 2~9mm size per ovary.

3. indicates high serum testosterone, free-testosterone or androstendione.

Blood sampling for measuring serum hormone levels should be done within the 10th day of menstrual cycle without follicles more than 10mm in size. Cushing's syndrome, androgen-secreting adrenal diseases and weight loss amenorrhea during recovery are diagnosis of exclusion.

Table 2: PCOS criteria by JSOG 2007.

The pregnancy and live birth rates were significantly lower in group A than those in the other two groups, and the live birth rate was significantly higher in group C than those in the other two groups (**Table 3**). The conceivable rate with clomiphene citrate was significantly higher in group C (27.7%) than that in the other two groups, and IVF was the most effective treatment for conception in all groups (**Table 3**). In group A, pregnant women had significantly higher AMH levels and were younger than those of non-pregnant women (**Table 4**). Of the pregnant women who experienced a miscarriage during the first pregnancy, 6, 14, and 12 women in groups A, B, and C, respectively, succeeded in giving birth until the end of 2020. The cumulative birth rates were significantly lower in group A and higher in group C than those in the other two groups (Table 5). The ages of women with cumulative birth were significantly younger than those with no birth in group A and group B; however, the difference was not significant in group C (**Table 5**).

-	Group A	Group B	Group C	
Pregnancy	57/123 (46.3%)*	168/248 (67.7%)	94/124 (75.8%)	
Abortion	17/57 (29.8%)	35/168 (20.8%)	13/94 (13.8%)	
Ectopic pregnancy	0	1/168 (0.6%)	2/94 (2.1%)	
Live birth	40/123 (32.5%)*	132/248 (53.2%)	79/124 (63.7%)**	
Success therapy to conceive				
Natural	21 (36.8%)	38 (22.6%)	19 (20.2%)	
Clomiphene citrate	3 (5.3%)	30 (17.9%)	26 (27.7%)**	
Gonadtropin	7 (12.3%)	13 (7.7%)	11 (11.7%)	
IVF	26 (45.6%)	87 (51.8%)	38 (40.4%)	
Note:*: p<0.0000 vs the other two groups by Chi-square test.				
**: p<0.05 vs the other two groups by Chi-square test.				

Table 3: Results of pregnancy in the three groups.

	-	Pregnancy	Non-pregnancy	
	Number of patients	57	66	
Group A (n=123)	AMH (median (minimum- maximum), ng/mL)	0.80 (0.02-1.33)*	0.60 (0.02-1.34)	
	Age (median (minimum- maximum), years)	37 (27-43)*	39 (30-45)	
Group B (n=248)	Number of patients	168	80	
	AMH (median (minimum- maximum), ng/mL)	2.76 (1.35-5.18)	2.63 (1.35-5.18)	
	Age (median (minimum- maximum), years)	35 (21-43)	35 (24-45)	
Group C (n=124)	Number of patients	94	30	
	AMH (median (minimum- maximum), ng/mL)	8.17 (5.19-68.3)	7.68 (5.29-34.5)	
	Age (median (minimum- maximum), years)	32 (23-42)	32.5 (22-41)	
Note: *: p<0.05 vs non-pregnancy by Mann-Whitney U test.				

Table 4: Comparison between pregnancy and non-pregnancy in the three groups.

-	-	Birth	No birth	
Group A (n=123)	Number of patients	46 (37.4%)*	77 (62.6%)	
	AMH (median (minimum- maximum), ng/mL)	0.76 (0.02-1.32)	0.63 (0.02-1.34)	
	Age (median (minimum- maximum), years)37 (27-41)**		39 (30-45)	
Group B (n=248)	Number of patients	146 (58.9%)*	102 (41.1%)	
	AMH (median (minimum- maximum), ng/mL) 2.79 (1.35-5.18)		2.66 (1.35-5.18)	
	Age (median (minimum- maximum), years)	34 (21-43)***	35 (24-45)	
Group C (n=124)	Number of patients	91 (73.4%)*	33 (26.6%)	
	AMH (median (minimum- maximum), ng/mL)	8.38 (5.19-68.3)	7.26 (5.29-34.5)	
	Age (median (minimum- maximum), years)	31 (23-42)	33 (22-41)	
Note:*:p<0.05 vs the other two groups by Chi-square test.				
p<0.0000. *p<0.05 vs no birth in each group by Mann-Whitney U test.				

Table 5: Comparison between the cumulative birth and no birth in the three groups.

Of 283 women with cumulative birth, 153 (54.1%) were followed in our hospital up to the end of birth. Women were significantly younger in group C than those in the other two groups (**Table 6**). GDM occurred more significantly in group B compared to data in the JSOG, and BMIs were significantly higher in GDM women (median: 22.6 Kg/m^2 , 17.9 - 30.4 [minimum-maximum]) than those in non-GDM women (20.2 Kg/m^2 , 16.0 - 29.1) in group B. Hypertensive disorders of pregnancy (HDP) occurred more significantly in groups A and B than those in the JSOG group (**Table 7**).

-	n (%)	AMH (ng/mL)	Age (years)	BMI (Kg/m ²)
Group A	27/46 (58.7%)	0.71 (0.02-1.32)	36 (27-41)	20.0 (16.6-27.1)
Group B	80/146 (54.8%)	2.83 (1.35-4.94)	34 (21-42)	20.6 (16.0-30.4)
Group C	46/91 (50.5%)	8.21 (5.23-30.36)	30 (23-42)*	20.3 (16.9-32.4)
Note: The numbers of AMH, age and BMI indicated the median with (minimum-maximum).				

*: p<0.05 vs group A and group B by Mann-Whitney U test.

Table 6: Characteristics of women followed until the end of deliveries in our hospital.

-	GDM	HDP	FGR	< 37weeks	Cesarean	< 2500g
Group A (n=27)	2 (7.4)	5 (18.5)*	1 (3.7)	4 (14.8)	7 (25.9)	5 (18.5)
Group B (n=80)	11 (13.8)*	11 (13.8)*	3 (3.8)	7 (8.8)	33 (41.3)	15 (18.8)
Group C (n=46)	2 (4.3)	3 (6.5)	3 (6.5)	3 (6.5)	10 (21.7)	7 (15.2)
Control (n=1,181,880)†	71,541 (6.1)	68,401 (5.8)	47,108 (4.0)	163,472 (13.8)	397,097 (33.6)	222,278 (18.8)
Note: Each number indicates the number of patients with each complication and its rate (%) in parenthesis.						
[†] : Control were the data from JSOG. Those were 18.8% of all delivery in Japan from 2014 to 2018.						
*: p<0.05 vs Control by Chi-square test.						

Table 7: Complications during pregnancy in the three groups.

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Discussion

This is the first report from Japan to analyze clinical data on fertility practices based on serum AMH levels. In addition, it is worth noting that the data were obtained from a single center with the same screening tests and the same treatment plan. Moreover, patient age, assisted reproductive technology (ART) receiving age, and age of peak ART cycle were the same as the Japanese standard where more than 440,000 ART cycles were performed every year to infertile women at a peak age of 40 [14]. Oocyte donation is limited, while embryo donation and host mother are prohibited. Moreover, the diagnostic criteria for PCOS are different from those of other countries.

In this study, the median age in the three groups was inversely related to AMH levels, as reported previously in Japanese women [15], and patients with serum AMH levels of less than first quartiles (1.35 ng/mL) were of advanced age and showed lower cumulative birth rates. However, successful pregnancies have been achieved in patients with serum AMH levels of 0.02 ng/mL. This result supports previous reports that low AMH levels do not imply that patients have to give up on pregnancy [16,17]. In this group, AMH is a useful numerical marker of growing follicles, but it is definitely inferior to age as a qualitative marker. This trend was also observed weakly in group B but not in group C. Patients with uterine lesions and unknown causes were more frequent than those in the other two groups, and approximately 40% of the pregnancies occurred during natural cycles with and without IUIs. However, 30% of pregnancies ended in miscarriage. These results seemed to be due to age in group A. Based on the results in (Table 4), the age of 38 may be an important turning point. We are now investigating the use of IVF and good embryos freezing first, followed by myomectomy, and subsequently thawed embryo transfer for aging infertile women with uterine myoma as a cause. Recently, we also have a new means of treatment. IVF, preimplantation genetic testing for aneuploidy, and subsequently, selecting a good embryo for transfer may reduce wasted time and increase successful pregnancies [18,19]. The Bologna consensus meeting suggested AMH<0.5-1.1 ng/mL (0.02-0.7 ng/mL in this study) as a decision value of POR [9].

In the current analysis, only 0.04% of the patients within this value became pregnant (data not shown). Although we agree with the value as an auxiliary diagnostic criterion for POR, it is very low to positively plan a treatment strategy for patients with low AMH in infertility practice. A serum AMH value of 1.35 ng/mL seems to be a beneficial criterion for diagnosing patients with pregnancy difficulty. Patients below this cut-off value were a population that is strongly influenced by specific causes of infertility and age. They also had a low rate of cumulative birth, which is the goal of infertility practice. This AMH value and the age of 38 years would accelerate the doctor's infertility strategy. New treatments such as written above may help them to give birth.

Conversely, how about the serum AMH value of 5.19 ng/ mL as a criterion for the high group? Patients in group C were young and showed the highest cumulative birth rates, and age or serum AMH levels did not affect the cumulative birth rate. Of the 50 patients with PCOS in the present analysis, 43 (86%) belonged to group C, and 13 of 26 pregnancies with clomiphene citrate in group C were women with PCOS (data not shown). We might tend to choose mild follicular stimulation to avoid OHSS because they were young enough not to accelerate the treatment strategy. In a meta-analysis, Iliodromiti et al. reported that 4.7 ng/mL (3.77 ng/mL in this study) was a good cutoff value of AMH with a sensitivity of 79.4% and specificity of 82.8% in diagnosing PCOS [6]. However, a universal cutoff for the AMH value for diagnosing PCOS has not yet been recommended by the ESHRE 2018 guidelines[20]. Matsuzaki et al. reported a relationship between serum AMH levels and PCOS in Japanese women and proposed 7.33 ng/mL AMH value as a cut-off for diagnosing PCOS [21].

Patients with PCOS in the present analysis also showed higher serum AMH levels that 86% of them had more than 5.19 ng/mL of serum AMH levels. These discrepancies may be due to differences in the measurement methods [21] and race. Recently, an interesting review was reported on racial and ethnic disparities in reproductive endocrinology and infertility [22]. Japanese patients with PCOS have lower BMIs compared to those in other countries. as reported previously [21] and in the present study. They also reported that lean Japanese patients with PCOS had significantly higher serum AMH levels than non-obese and obese Japanese patients with PCOS [21]. The most important factor in determining the upper cut-off value of serum AMH is to predict the response of the ovaries to ovarian stimulation therapy. From this perspective, it is important to know the value that is useful for diagnosing PCOS. In the present study, 7 patients with PCOS belonged to group B. Moreover, 28 patients with polycystic ovaries who were not PCOS by JSOG criteria but PCOS by Rotterdam criteria [23] were enrolled in this study. Of the 28 patients, 9 (32.1%) were included in group B. Their ovaries showed hypersensitivity to ovarian stimulation therapy (data not shown). The upper cut-off value of serum AMH might be set to be lower than 5.19 ng/mL.

Recently, there has been a lot of focus on pre-conception management in Japan. PCOS is well known to be associated with high serum AMH levels [5,6] and insulin resistance [11,12]. We examined serum AMH levels as a pre-conception marker for GDM. Although the number of patients was small, GDM seemed to relate not to AMH but BMI. It has been reported that obese patients with PCOS show insulin resistance, but non-obese and lean PCOS patients have mild or no insulin resistance [24,25]. HDP complications occurred more frequently in women with less than 5.19 ng/mL of serum AMH levels that seemed to be due to their age.

Conclusion

In the present analysis, the lower criterion (1.35 ng/mL of serum AMH value) is appropriate for selecting patients with difficulty in pregnancy. In these patients, the aging effect was much greater, especially in those more than 38 years old. Conversely, the upper criterion (5.19 ng/mL) seemed to be a good choice for easily conceivable and OHSS high-risk patients like those with PCOS in the present study. However, this upper value fluctuates depending on the measurement system and race. Between nations with different measurement systems and different fertility practice, it is necessary to set serum AMH criteria that are appropriate for the field. To comment on the usefulness as a pre-conceptional marker for GDM, the number of cases reviewed was too small in this study.

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