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ARTICLE

The correlation between AMH and number of embryos in POSEIDON groups: a retrospective cohort study

BIOGRAPHY

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KEY MESSAGE

For POSEIDON criteria Group 3 and 4 populations with poor prognosis in ART treatment, the number of available embryos per stimulation cycle can be predicted by AMH to determine its potential reproductive prognosis. As an evaluation for patients with poor ovarian reserve (POR) or reduced ovarian reserve before ART treatment, it can reduce abandonment of treatment due to underestimation or multiple ineffective treatments.

ABSTRACT

Research question: What is the association between serum anti-Müllerian hormone (AMH) concentrations and the number of utilizable embryos obtained per stimulation cycle of IVF/intracytoplasmic sperm injection (ICSI) in POSEIDON Groups 3 and 4?

Design: Retrospective cohort study of 412 cycles, in which patients in POSEIDON Groups 3 and 4 (antral follicle count [AFC] ≤5 and AMH <1.2 ng/ml) underwent complete IVF/ICSI treatment cycles in the Reproductive Center of the First Affiliated Hospital of Xinjiang Medical University between January 2017 and March 2019. Patients underwent IVF/ICSI treatment using either progestin-primed ovarian stimulation (PPOS) or gonadotrophin-releasing hormone (GnRH) antagonist protocol as ovarian stimulation protocol.

Results: Three models were established to analyse the correlation between AMH and the number of utilizable embryos in this study. After adjusting for covariates (age, baseline FSH, stimulation protocol and AFC), the number of embryos increased by 0.1 (95% confidence interval [CI] 0.06–0.14) with each increment of 0.1 ng/ml in AMH concentration. AMH was transformed from a continuous variable to a categorical variable (through trisection of AMH concentrations) and for the sensitivity analysis it was found that the number of embryos in the high AMH group (0.52–1.19 ng/ml) was 0.62 (95% CI 0.37–0.97) higher than in the low AMH group (0.06–0.24 ng/ml).

Conclusions: High AMH in patients in POSEIDON Groups 3 and 4 was found to be associated with an increase in the number of available embryos in IVF/ICSI. The potential reproductive prognosis can be assessed by AMH, to reduce the abandonment of treatment due to underestimation or to implement multiple ineffective stimulation cycles of treatment.

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KEYWORDS

Anti-Müllerian hormone
Antral follicle count
IVF–embryo transfer
Number of embryos
Poor ovarian response
POSEIDON criteria

INTRODUCTION

One of the significant challenges in IVF/intracytoplasmic sperm injection (ICSI) treatment is to manage women with impaired ovarian reserve. These 'poor responders' usually have relatively low live birth rates (*Polyzos et al., 2018*). Thus, the POSEIDON Group proposed a more precise classification of 'low-prognosis women' in 2016 (*Humaidan et al., 2016*), which grouped women according to their age, ovarian reserve tests (anti-Müllerian hormone [AMH] or antral follicle count [AFC]), and previous ovarian response after ovarian stimulation. The POSEIDON criteria have improved the homogeneity and comparability of clinical studies and can potentially help clinicians provide better treatments for these low-prognosis women (*Conforti et al., 2019*; *Humaidan et al., 2016*).

Poor ovarian reserve (POR) limits the success of treatment with assisted reproductive technologies (ART) (*Badawy et al.,2011*). Especially for patients in POSEIDON Groups 3 and 4, assessment and treatment are difficult before IVF/ICSI treatment (*Esteves et al., 2019*). Among various traditional biomarkers for predicting ovarian reserve, serum AMH is the preferred marker (Moolhuijsen and Visser, 2020; *Seifer et al., 2002*; *Tal and Seifer, 2017*). AMH is produced by the granulosa cells in adult women, reducing with age (*La et al., 2010*). Recent studies have shown that AMH predicts POR better than AFC and FSH. The AMH test is readily available and AMH has been shown to vary only slightly throughout the menstrual cycle (*Somunkiran et al., 2007*).

In IVF/ICSI treatment, low AMH predicts a lower number of oocytes. However, recent studies (*Baker et al., 2018*; *Dewailly et al.,2019*) have found that even if AMH concentrations are ultra-low, pregnancy may occur. AMH has a low predictive value for pregnancy rate after IVF/ICSI (*Seifer et al., 2016*). Whether AMH can be used as a predictor in patients with POR remains controversial.

According to POSEIDON's new concept (*POSEIDON Group, 2016*) for managing patients with low prognosis during ART treatment, the criterion for measuring success is to increase the probability of transfer of at least one euploid embryo. To achieve the purpose of fertility, utilizable embryos must first be formed. There are no further reports on whether AMH can predict the number of embryos to determine their potential reproductive prognosis. This study aimed to discuss whether AMH could predict the number of available embryos obtained per stimulation cycle in POSEIDON Group 3 and 4 patients, providing valuable data to guide IVF/ICSI pretreatment.

MATERIALS AND METHODS

Study design

In this single-site retrospective cohort study of 412 cycles, data were obtained from women who underwent IVF/ICSI treatment at the Reproductive Center of the First Affiliated Hospital of Xinjiang Medical University in China. FIGURE 1 shows the flow chart of patient selection. POSEIDON criteria Groups 3 or 4 (AFC ≤5 and AMH <1.2 ng/ml) received a total of 409 cycles of progestin-primed ovarian stimulation (PPOS) or gonadotrophin-releasing hormone (GnRH) antagonist protocol as ovarian stimulation protocol between January 2017 and March 2019 and were followed until the end of the cycle. The exclusion criteria included: presence of systemic diseases (one cycle); premature ovarian failure (one cycle); and women who had their eggs cryopreserved (one cycle).

This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (approval number: 20170518-02; approved 23 May 2017).

Quantitative variables

Serum AMH test

For the automatic chemiluminescence detection analyser (Chongqing Coside Biotechnology Co., Ltd, KAESER6600) and the AMH assay kit (chemiluminescent immunoassay) (Guangzhou Kangrun Biotech Co., Ltd, Guangzhou, China) used, the limit of detection is 0.06 ng/ml (range 0.07–18 ng/ml), the correlation coefficient (r) should not be less than 0.99, and the coefficient of variation of the inter-batch

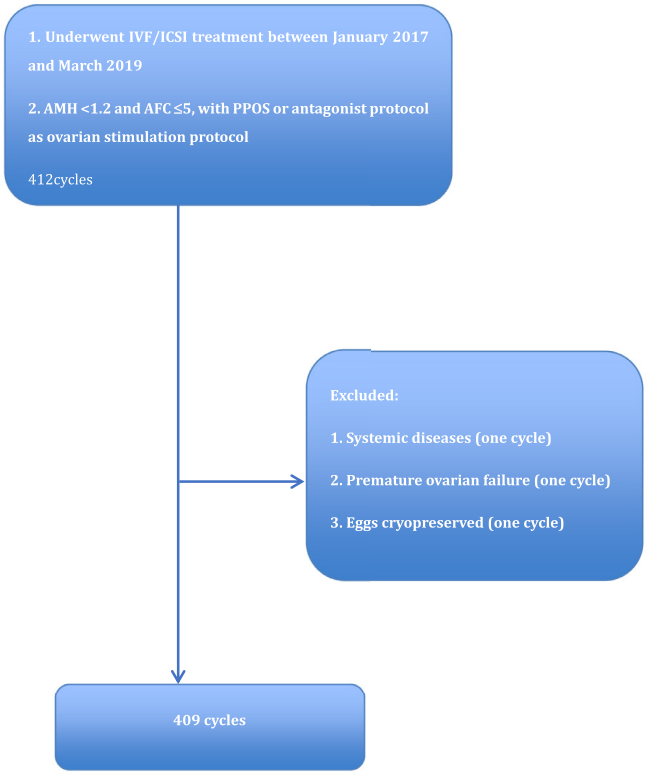

FIGURE 1 Flow chart of patient recruitment. IVF/ICSI was performed between January 2017 and March 2019. POSEIDON criteria Group 3 or 4 were met and PPOS or antagonist protocols were used as ovarian stimulation protocols in the study. AFC = antral follicle count; AMH = anti-Müllerian hormone; ICSI = intracytoplasmic sperm injection; PPOS = progestin-primed ovarian stimulation.

difference is <15%. All blood samples were tested on the day of collection or within 3 days of collection (pending testing at 2–8°C).

Antral follicular count

AFC (*Broekmans et al., 2010*) is defined as the sum of follicles with a 2–10 mm diameter in the ovary. On days 2 to 4 of the menstrual cycle, AFC was measured at the Reproductive Center by transvaginal ultrasound, by two or three specialists each with more than 10 years of experience.

Number of embryos

The primary endpoint was the number of utilizable embryos (a continuous variable). This study only included patients who received PPOS or antagonist protocol as the ovarian stimulation protocol.

Stimulation protocol

Patients started daily gonadotrophin treatment from the second or third day of their menstrual cycle, with dosage adjusted according to their ovarian response. Patients who received the PPOS protocol also took concomitant oral medroxyprogesterone acetate 10 mg/day until the final gonadotrophin injection. In patients who received the antagonist protocol, GnRH antagonist (0.125 mg or 0.25 mg Cetrotide®) was added at the appropriate time according to the oestradiol level, follicle size and LH value 3 days after the stimulation. Ultrasound examination and serum sex hormone tests were used for cycle monitoring. When two or more follicles grew to 18 mm, 4000–10,000 IU human chorionic gonadotrophin (HCG) was given to trigger ovulation. After IVF/ICSI using the retrieved oocytes, embryos were cultured to day 3 and then cryopreserved or transferred according to their condition. Ovarian stimulation cycles included ovarian stimulation, aspiration, insemination and production of all embryos. Cycle cancellation before oocyte retrieval was considered to be no oocyte retrieval for inclusion in the analysis.

Continuous variables included age, body mass index (BMI), AFC, infertility duration, basal FSH, basal oestradiol, basal LH, duration of stimulation, the total dose of gonadotrophin, number of oocytes and number of utilizable embryos. Categorical variables included aetiology of infertility, stimulation protocol and fertilization (IVF/ICSI).

Statistical methods

The statistical analysis was conducted with AMH as the target-independent variable and number of embryos as the dependent variable. Continuous variables were expressed as mean ± SD or median (the 25th–75th percentile). Categorical variables were expressed as frequency or percentage. Differences among groups were compared using single-factor analysis of variance (ANOVA) and chi-squared test. Variables in skewed distribution were tested using the Kruskal–Wallis method. The data analyses were conducted on three levels: (i) the correlation between AMH and number of utilizable embryos (linear or non-linear); (ii) which factors might interfere with or affect the correlation between AMH and number of utilizable embryos; (iii) what is the real correlation between AMH and number of utilizable embryos after adjustment for interfering factors or after stratified analysis? A generalized additive model (GAM) was used to estimate the independent relationship of association between AMH and the number of utilizable embryos (FIGURE 2). Smoothing linear regression model GAM was adjusted using R software to relate the number of utilizable embryos depending on AMH (*Hastie and Tibshirani, 1990*; *R Development Core Team, 2008*). The results of this analysis are displayed graphically. The statistical software package R (http://www.R-project.org, the R Foundation) and Empower (R) (www.empowerstats.com, X and Y solutions, Inc. Boston, MA, USA) were used for data analyses. Two-way $P < 0.05$ indicated statistical significance.

RESULTS

Baseline characteristics of the study population

A total of 409 IVF/ICSI cycles were included in the analysis. The study population was divided into three near-equal ($n = 135$, $n = 134$ and $n = 140$) groups according to AMH concentration. The baseline characteristics of participants are represented in TABLE 1. The three groups were: low AMH group (AMH 0.06–0.24 ng/ml, $n = 135$), intermediate AMH group (AMH 0.25–0.51 ng/ml, $n = 134$) and high AMH group (AMH 0.52–1.19 ng/ml, $n = 140$). There were no statistical differences in BMI ($P = 0.096$), duration of infertility ($P = 0.28$), ovarian stimulation cycles ($P = 0.731$), the total dose of gonadotrophin ($P = 0.861$) and oestradiol concentration on HCG day ($P = 0.22$) among the three groups. Across the three groups, significant trends were seen when comparing the high AMH group to the lower AMH groups. Higher AMH correlated with decreased age ($P = 0.031$), increased basal FSH ($P < 0.001$), decreased AFC ($P < 0.001$) and a decreased percentage of ovarian stimulation with the PPOS protocol ($P = 0.044$). As shown in TABLE 1, the number of oocytes retrieved ($P < 0.001$), the number of metaphase II (MII) oocytes ($P < 0.001$) and the number of available embryos ($P < 0.001$) decreased significantly with decreasing AMH.

AMH was linearly correlated with the number of utilizable embryos

From left to right in FIGURE 2, as the AMH concentration increased, the number of utilizable embryos increased. The trend of gradual increase in the number of utilizable embryos was statistically significant ($P < 0.001$).

The correlation between AMH and the number of utilizable embryos

Three models were established to analyse the correlation between AMH and the number of embryos in this study (as shown in TABLE 2). For the sensitivity analysis AMH was transformed from a continuous variable to a categorical variable (through trisection of AMH concentration). The number of utilizable embryos in the high AMH group (0.52–1.19 ng/ml) was 0.89 (95% CI 0.60–1.18, $P < 0.0001$), higher than in the low AMH group (0.06–0.24 ng/ml, reference). After adjusting covariates listed in TABLE 1, namely age, baseline FSH, stimulation protocol and AFC, it was found that the number of utilizable embryos in the high AMH group was 0.62 (95% CI 0.37–0.97, $P < 0.0001$) higher than in the low AMH group (reference). The number of utilizable embryos in the Adjust II Model increased by 0.1 (95% CI 0.06–0.14) with each increment of 0.1 ng/ml in AMH concentration.

DISCUSSION

The prognosis of patients with POR is poor because their ovarian reserve decreases and age-related aneuploidy increases, and their management is challenging (*Esteves et al., 2019*). Many clinicians adopt a 'trial and error' strategy (*Humaidan et al., 2019*) because of the lack of evidence and the population heterogeneity. This study used the

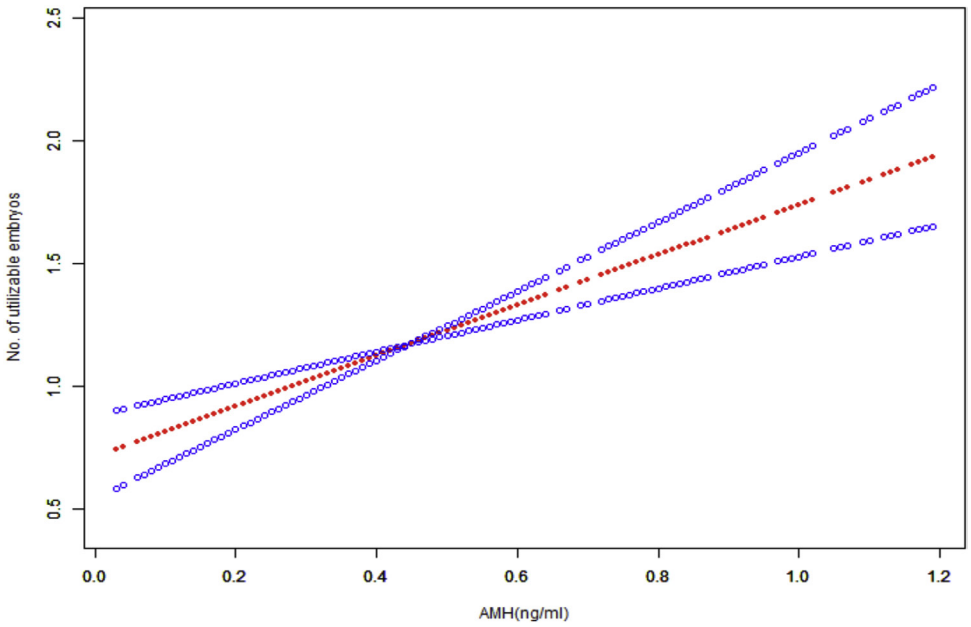

FIGURE 2 Association between AMH and the number of utilizable embryos. Linear association between AMH and the number of utilizable embryos was found in a generalized additive model (GAM). Red line represents the fit between variables. Blue bands represent the 95% confidence interval from the fit. All adjusted for age, AFC, baseline FSH and ovarian stimulation protocol. AFC = antral follicle count; AMH = anti-Müllerian hormone.

POSEIDON criteria (*Esteves et al., 2019*) to include the Group 3 and 4 populations, with better population homogeneity and clear characteristics to distinguish them from other patients. Before implementing ART, it is essential to provide counselling for infertile couples through easier access, more economical and objective indicators, such as age, AMH and AFC, in daily practice.

AFC and AMH are widely used as markers of ovarian reserve, and AMH has recently been shown to be a better predictor of POR. Early studies have found that AMH variation is limited both within and between cycles (*La Marca et al., 2007*; *Van Disseldorp et al., 2010*). AMH has been observed to vary minimally throughout the menstrual cycle (*Gracia et al., 2018*), and kits for its detection are readily available. There is no uniform international reference standard for AMH detection, and it varies between different testing methods and laboratories (*Nelson et al., 2015*). However, this study was conducted in one reproductive centre, and the test methods were consistent, so the reliability of the results was not affected.

AFC, detected by vaginal ultrasound on days 2–4 of the menstrual cycle, has the advantage of being easily observable and can be used to predict the risk of POR (*Tal and Seifer, 2017*). Although it has been reported that AFC varies from observer to observer (*Andersen et al.,2015*; *Iliodromiti et al.,2015*), this study was performed by two or three reproductive physicians with extensive experience of ultrasound, which mitigates the occurrence of bias.

This study showed that younger age, lower basal FSH and higher AFC were associated with higher AMH in Groups 3 and 4 of the POSEIDON criteria. In IVF/ICSI, AMH was independently and linearly positively associated with the utilizable embryo number after adjusting for other covariates.

The main marker of success in patients with POR is cumulative live birth rate. That is, at least one euploid embryo transfer per cycle is required for a successful pregnancy. *Yuan Li et al. (2019)* concluded that in POSEIDON Groups 3 and 4, lower AFC and expected decrease in the number of euploid embryos transferred were the main reasons for poor outcome. The retrieval of a large number of oocytes (which will increase the likelihood of having at least one euploid embryo) is difficult in POSEIDON Groups 3 and 4 women (*Haahr et al., 2018*). In POR, it is the quantity not quality that limits the success of ART in these patients (*Morin et al.,2018*), showing the importance of the number of embryos for patients with POR. The findings of this study showed that an increase in AMH of 0.1 ng/ml would obtain 0.09 more embryos. Analysis of patients showed that patients with AMH values >0.52 ng/ml obtained 0.62 more embryos than those with AMH <0.25 ng/ml. This will provide a basis for estimating their potential reproductive prognosis.

The following factors may contribute to the controversy over using AMH as a predictor of IVF/ICSI treatment. (i) Some studies (*Tal et al., 2018*; *Zhang et al., 2019*) did not set limitations for the included population. Participants included not only poor responders but also normal responders and even high responders. There was also no limitation on the AMH concentration, and therefore, the inclusion of different populations may have led to different results. (2) Heterogeneity of the population may be another factor. Even those with only a poor response mainly used the Bologna criteria, classifying patients with significant biological differences into one group.

The current study has some clinical value. Firstly, it shows that when ruling out the influence of age, BMI, AFC and

TABLE 1 BASELINE CHARACTERISTICS OF THE STUDY POPULATION

Characteristic	AMH (ng/ml)			*P*-value
	AMH 0.06–0.24	**AMH 0.25–0.51**	**AMH 0.52–1.19**	
No. of participants	135	134	140	
Age (years)	39.15 ± 5.22	37.96 ± 5.06	37.59 ± 4.96	0.031
Infertility duration (years)	5.59 (5.26) 4.00 (2.00–7.00)	4.09 (2.73) 3.00 (2.00–6.00)	4.17 (3.28) 3.00 (2.00–5.00)	0.128
BMI (kg/m^2)	24.21 ± 3.27	23.36 ± 3.60	23.65 ± 2.88	0.096
Baseline FSH (mIU/ml)	12.30 ± 6.11	10.43 ± 4.79	9.94 ± 4.92	<0.001
Baseline oestradiol (pmol/l)	151.65 (222.14) 87.00 (50.58–147.50)	128.65 (84.57) 105.36(69.00–174.10)	147.72 (254.78) 107.50 (52.31–165.00)	0.607
LH (mIU/ml)	4.19 (2.79) 3.40 (2.43–5.21)	3.88 (2.48) 3.42 (2.27–4.85)	4.65 (11.82) 3.31 (2.27–4.80)	0.67
AMH (ng/ml)	0.12 ± 0.06	0.39 ± 0.08	0.82 ± 0.21	<0.001
Oestradiol on HCG day (pmol/l)	2187.76 (1631.55) 1842.00 (1099.46–2650.52)	2263.22 (1782.09) 1747.00 (945.00–3044.03)	2727.86 (2368.41) 1987.00 (1174.42–3386.00)	0.22
AFC	2.61 (1.29) 2 (2–4)	3.09 (1.27) 3 (2–4)	3.39 (1.29) 3.50 (2–5)	<0.001
Days on gonadotrophin	9.20 ± 2.43	9.51 ± 2.52	9.08 ± 2.42	0.321
Total gonadotrophin (IU)	2297.29 ± 1112.29	2363.53 ± 1184.23	2294.02 ± 1230.68	0.861
Stimulation protoco				0.044
Antagonist protocol	24 (17.8)	32 (23.9)	42 (30)	
PPOS protocol	111 (82.2)	102 (76.1)	98 (70)	0.549
Diagnosis				
Primary infertility	53 (39.3)	47 (35.1)	58 (41.4)	
Secondary infertility	82 (60.7)	87 (64.4)	82 (58.6)	
Fertilization[a]				0.036
IVF	96 (81.3)	96 (76.80)	92 (67.7)	
ICSI	22 (18.6)	29 (23.20)	44 (32.3)	
No. of oocytes retrieved	1.83 (1.40)	2.72 (1.99)	4.26 (3.04)	<0.001
	1.00 (1.00–2.00)	2.00 (1.00–4.00)	3.00 (2.00–5.00)	
No. of MII	1.65 (1.24)	2.49 (1.92)	3.59 (2.63)	<0.001
	1 (1–2)	2 (1–3)	3 (2–5)	
No. of utilizable embryos	0.73 (0.90)	1.14 (1.34)	1.62 (0.36)	<0.001
	0 (0–1)	1 (0–2)	2 (0–2)	
Ovarian stimulation cycle				0.731
Single cycle	57 (42.2)	54 (40.3)	63 (45.0)	
Multiple cycles	78 (57.8)	80 (59.7)	77 (55.0)	

Continuous variables are described as means ± SD or median (25th–75th percentile) and categorical data are presented as number and percentage.

The differences between groups were compared using one-way analysis of variance (ANOVA) for continuous data and chi-squared tests for categorical variables.

The Kruskal-Wallis test was applied for variables with a skewed distribution.

AFC = antral follicle count; AMH = anti-Müllerian hormone; B-E_2 = ; B-FSH = ; BMI = body mass index; HCG-E2 = human chorionic gonadotrophin; ICSI = intracytoplasmic sperm injection; MII = metaphase II; PPOS = progestin-primed ovarian stimulation.

[a] In the case of cycle cancellation, no oocyte retrieval or no mature oocytes, IVF/ICSI implementation was cancelled.

stimulation protocol, an independent linear correlation was observed between AMH and the number of embryos in POSEIDON Groups 3 and 4 women undergoing IVF/ICSI treatment. Secondly, low-prognosis patients could be identified through clear markers such as age, AMH and AFC. The results could provide physicians with information about these patients' potential reproductive prognosis, and how many cycles of IVF/ICSI need to be treated to lead to better results.

The strengths of this study include that (i) a highly homogeneous study population was recruited; (ii) this is an observational study, which is usually prone to having confounders; however, these confounding factors were minimized in this study by the use of strict statistical adjustment; (iii) robust conclusions were obtained by analysing the data of different subgroups. AMH was used as

TABLE 2 RELATIONSHIP BETWEEN AMH AND THE NUMBER OF UTILIZABLE EMBRYOS IN DIFFERENT MODELS

Exposure	Non-adjusted[a]	*P*-value	Adjust I[b]	*P*-value	Adjust II[c]	*P*-value
AMH (ng/ml)						
AMH (0.06–0.24)	Reference		Reference		Reference	
AMH (0.25–0.51)	0.41 (0.12, 0.71)	0.0060	0.31 (0.02, 0.60)	0.0397	0.27 (0.03, 0.56)	0.0747
AMH (0.52–1.19)	0.89 (0.60, 1.18)	<0.0001	0.73 (0.43, 1.02)	<0.0001	0.62 (0.37, 0.97)	<0.0001
AMH per 0.1 ng/ml	0.13 (0.09, 0.16)	<0.0001	0.11 (0.07, 0.14)	<0.0001	0.10 (0.06, 0.14)	<0.0001

Data are presented as increase in number of utilizable embryos (95% CI).

AFC = antral follicle count; AMH = anti-Müllerian hormone.

[a] Non-adjusted model: other co-variants were not adjusted.

[b] Adjust I model: age and AFC were adjusted.

[c] Adjust II model: age, AFC, baseline FSH and ovarian stimulation protocol were adjusted.

a stratification variable to observe the trends in number of embryos (TABLE 2). The study found a linear correlation between AMH and number of embryos per stimulation cycle and the specific quantitative association between them.

This study's limitation is its retrospective nature. The results were obtained in a homogeneous population of patients who used a PPOS or an antagonist protocol as the ovarian stimulation protocol and so cannot be extrapolated to other populations. However, the data are consistent with previous studies. Future prospective studies in the entire POSEIDON population may be needed to validate the results.

It was found that high AMH in patients in POSEIDON Groups 3 and 4 was associated with an increase in the number of available embryos in IVF/ICSI. Reproductive prognosis can be predicted through AMH to reduce treatment abandonment due to underestimation or implementing multiple ineffective stimulation cycles.

REFERENCES

Andersen, R.A., Anckaert, E., Bosch, E., Dewailly, D., Dunlop, C.E., Fehr, D., Nardo, L., Smitz, J., Tremellen, K., Denk, B., Geistanger, A., Hund, M. **Prospective study into the value of the automated Elecsys antimullerian hormone assay for the assessment of the ovarian growing follicle pool.** Fertil. Steril. 2015; 103: 1074–1080

Badawy, A., Wageah, A., El Gharib, M., Osman, E.E. **Prediction and diagnosis of poor ovarian response: the dilemma.** J. Reprod. Infertil. 2011; 12: 241–248

Baker, V.L., Gracia, C., Glassner, M.J., Schnell, V.L., Doody, K., Coddington, C.C., Shin, S.S., Marshall, L.A., Alper, M.M., Morales, A.J., Pavone, M.E., Behera, M.A., Zbella, E.A., Shapiro, B.S., Straseski, J.A., Broyles, D.L. **Multicenter evaluation of the Access AMH antimüllerian hormone assay for the prediction of antral follicle count and poor ovarian response to controlled ovarian stimulation.** Fertil. Steril. 2018; 110: 506–513

Broekmans, F.J., deZiegler, D., Howles, C.M., Gougeon, A., Trew, G., Olivennes, F. **The antral follicle count: practical recommendations for better standardization.** Fertil. Steril. 2010; 94: 1044–1051

Conforti, A., Esteves, S.C., Picarelli, S., Iorio, G., Rania, E., Zullo, F., De Placido, G., Alviggi, C. **Novel approaches for diagnosis and management of low prognosis patients in assisted reproductive technology: the POSEIDON concept.** Panminerva Med. 2019; 61: 24–29

Dewailly, D., Laven, J. **AMH as the primary marker for fertility.** Eur. J. Endocrinol. 2019; 1816: 45–51

Esteves, S.C., Carvalho, J.F., Martinhago, C.D., Melo, A.A., Bento, F.C., Humaidan, P., Alviggi, C. **POSEIDON (Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number) Group. Estimation of age-dependent decrease in blastocyst euploidy by next generation sequencing: development of a novel prediction model.** Panminerva Med. 2019; 61: 3–10

Esteves, S.C., Alviggi, C., Humaidan, P., Fischer, R., Andersen, C.Y., Conforti, A., Bühler, K., Sunkara, S.K., Polyzos, N.P., Galliano, D., Grynberg, M., Yarali, H., Özbek, I.Y., Roque, M., Vuong, L.N., Banker, M., Rienzi, L., Vaiarelli, A., Cimadomo, D., Ubaldi, F.M. **The POSEIDON Criteria and Its Measure of Success Through the Eyes of Clinicians and Embryologists.** Front Endocrinol. (Lausanne) 2019; 10: 814

Gracia, C.R., Shin, S.S., Prewitt, M., Chamberlin, J.S., Lofaro, L.R., Jones, K.L., Clendenin, M., Manzanera, K.E., Broyles, D.L. **Multi-center clinical evaluation of the Access AMH assay to determine AMH levels in reproductive age women during normal menstrual cycles.** J. Assist. Reprod. Genet. 2018; 35: 777–783

Haahr, T., Esteves, S.C., Humaidan, P. **Individualized controlled ovarian stimulation in expected poor-responders: an update.** Reprod. Biol. Endocrinol. 2018; 16: 20

Hastie, T., Tibshirani, R. 1990 **Generalized Additive Models.** Chapman and Hall Boca Raton

Humaidan, P., Alviggi, C., Fischer, R., Esteves, S.C. **The novel POSEIDON stratification of 'low prognosis patients in assisted reproductive technology' and its proposed marker of successful outcome.** F1000Res 2016; 5: 2911–2913

Humaidan, P., La Marca, A., Alviggi, C., Esteves, S.C., Haahr, T. **Future Perspectives of POSEIDON Stratification for Clinical Practice and Research.** Frontiers in Endocrinology 2019; 10: 439–441

Iliodromiti, S., Anderson, R.A., Nelson, S.M. **Technical and performance characteristics of anti-mullerian hormone and antral follicle count as biomarkers of ovarian response.** Hum. Reprod. Update 2015; 21: 698–710

La Marca, A., Sighinolfi, G., Radi, D., Argento, C., Baraldi, E., Artenisio, A.C., Stabile, G., Volpe, A. **Anti-mullerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART).** Hum. Reprod. Update 2010; 16: 113–130

la Marca, A., Giulini, S., Tirelli, A., Bertucci, E., Marsella, T., Xella, S., Volpe, A. **Anti-Mullerian hormone measurement on any day of the menstrual cycle strongly predicts ovarian response in assisted reproductive technology.** Hum. Reprod. 2007; 22: 766–771

Morin, S.J., Patounakis, G., Juneau, C.R., Neal, S.A., Scott, R.T.Jr., Seli, E. **Diminished ovarian reserve and poor response to stimulation in patients <38 years old: a quantitative but not qualitative reduction in performance.** Hum. Reprod. 2018; 33: 1489–1498

Nelson, S.M., Pastuszek, E., Kloss, G., Malinowska, I., Liss, J., Lukaszuk, A., Plociennik, L., Lukaszuk, L. **Two new automated, compared with two enzyme-linked immunosorbent, anti-mullerian hormone assays.** Fertil. Steril. 2015; 104: 1016–1021

Polyzos, N.P., Drakopoulos, P., Parra, J., Pellicer, A., Santos-Ribeiro, S., Tournaye, H., Bosch, E., Garcia-Velasco, J. **Cumulative live birth rates according to the number of oocytes retrieved after the first ovarian stimulation for in vitro fertilization/intracytoplasmic sperm injection: a multicenter multinational analysis including ~15,000 women.** Fertil. Steril. 2018; 110: 661–670

POSEIDON Group (Patient-Oriented Strategies Encompassing Individualized Oocyte Number). Alviggi, C., Andersen, C.Y., Buehler, K., Conforti, A., De Placido, G., Esteves, S.C., Fischer, R., Galliano, D., Polyzos, N.P., Sunkara, S.K., Ubaldi, F.M., Humaidan, P. **A new more detailed stratification of low responders to ovarian stimulation: from a poor ovarian response to a low prognosis concept.** Fertil. Steril. 2016; 105: 1452–1453

R Development Core Team. 2008 **R: A language and environment for statistical computing.** R Foundation for Statistical Computing Vienna, Austria

Seifer, D.B., MacLaughlin, D.T., Christian, B.P., Feng, B., Shelden, R.M. **Early follicular serum mullerian-inhibiting substance levels are associated with ovarian response during assisted reproductive technology cycles.** Fertil. Steril. 2002; 77: 468–471

Seifer, D.B., Tal, O., Wantman, E., Edul, P., Baker, V.L. **Prognostic indicators of assisted reproduction technology outcomes of cycles with ultralow serum antimullerian hormone: a multivariate analysis of over 5,000 autologous cycles from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System database for 2012–2013.** Fertil. Steril. 2016; 105: 385–393

Somunkiran, A., Yavuz, T., Yucel, O., Ozdemir, I. **Anti-mullerian hormone levels during hormonal contraception in women with polycystic ovary syndrome.** Eur. J. Obstet. Gynecol. Reprod. Biol. 2007; 134: 196–201

Tal, R., Seifer, D.B. **Ovarian reserve testing: a user's guide.** Am. J. Obstet. Gynecol. 2017; 217: 129–140

Tal, R., Seifer, D.B., Wantman, E., Baker, V., Tal, O. **Antimullerian hormone as a predictor of live birth following assisted reproduction: an analysis of 85,062 fresh and thawed cycles from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System database for 2012–2013.** Fertil. Steril. 2018; 19: 258–265

van Disseldorp, J., Lambalk, C.B., Kwee, J., Looman, C.W., Eijkemans, M.J., Fauser, B.C. **Broekmans FJ Comparison of inter- and intra-cycle variability of anti-mullerian hormone and antral follicle counts.** Hum. Reprod. 2010; 25: 221–227

Yuan, Li, Xiaofeng, Li, Xiaoyi, Yang, Sufen, Cai, Guangxiu, Lu, Ge, Lin, Peter, Humaidan, Fei, Gong **Cumulative Live Birth Rates in Low Prognosis Patients According to the POSEIDON Criteria: An Analysis of 26,697 Cycles of *in vitro* Fertilization/ Intracytoplasmic Sperm Injection.** Front Endocrinol (Lausanne) 2019; 10: 642–647

Zhang, B., Meng, Y., Jiang, X., Liu, C., Zhang, H., Cui, L., Chen, Z.J. **IVF outcomes of women with discrepancies between age and serum anti-Müllerian hormone levels.** Reproductive Biology and Endocrinology 2019; 17: 9–12

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