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ASSISTED REPRODUCTION

Serum anti-Müllerian hormone predicts ovarian response and cycle outcome in IVF patients

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Abstract
Purpose This prospective study was designed to investigate whether anti-Müllerian hormone (AMH) levels at basal and ovulation triggering day are associated with ovarian response and pregnancy outcome for in vitro fertilization (IVF).
Method 60 infertility women undergoing IVF were prospectively studied. On day 3 of the menstrual cycle (D3), measurements of AMH, inhibin B, FSH, LH, and E2 and ultrasound evaluation of antral follicle count (AFC) were performed. Serum AMH and inhibin B levels were remeasured on the day of hCG administration (DhCG). The outcome measures were the number of retrieved oocytes and clinical pregnancy.
Results Number of retrieved oocytes was statistically significant and correlated with D3 AMH, AFC, DhCG AMH, DhCG inhibin B, FSH, and age (r=0.885, 0.874, 0.742, 0.732, −0.521, −0.385, respectively). Statistically significant differences were found between pregnant and non-pregnant women regarding D3 AMH and AFC. Multiple regression analysis for prediction of pregnancy showed D3 AMH to be a good predictor of clinical pregnancy.
Conclusion AMH correlates better than age, FSH, and inhibin B with the number of retrieved oocytes. Serum basal AMH may offer a better prognostic value for clinical pregnancy than other currently available markers of IVF outcome in our preliminary study.

Keywords Anti-Müllerian hormone · IVF · Ovarian reserve · Pregnancy

Capsule Serum basal AMH correlates better than age, FSH, and inhibin B with the number of retrieved oocytes and may offer a better prognostic value for clinical pregnancy in IVF cycles.

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Introduction

Assessment of "ovarian reserve" is important before in vitro fertilization (IVF) treatment is undertaken. Identification of both low and high responders prior to ovulation induction allows physicians to optimize stimulation protocols to decrease cycle cancellation rate and side effects, such as ovarian hyperstimulation syndrome (OHSS).Traditionally, day 3 follicle-stimulating hormone (FSH), estradiol (E2), and inhibin B levels have been used as indicators of ovarian reserve. However, their predictive values remain somewhat controversial and require specific menstrual days for accurate analysis [1–3]. Furthermore, several investigators have reported the usefulness of ovarian volume [4, 5] and antral follicle count (AFC) [6, 7] in predicting ovarian response to hormone stimulation. Nonetheless, ultrasonography is subjective, and the interpretation of the observations may not be consistent [8]. Recently, a new endocrine marker, anti-Müllerian hormone (AMH), has been evaluated by several groups as a marker of ovarian response [9–16].

Anti-Müllerian hormone (AMH), also called Müllerian inhibiting substance, belongs to the transforming growth factor-β (TGF-β) superfamily, and it is considered a local growth factor and a cellular differentiation factor [17]. In women, AMH is exclusively produced in the ovary by the

granulosa cells surrounding preantral and small antral follicles [18, 19]. Hence, it is thought that serum AMH levels are a reflection of the size of the growing cohort of small follicles [11, 20], which in turn reflects the number of residual primordial follicles, or the ovarian reserve.

Growing evidence indicates that serum AMH levels have showed greater sensitivity to ovarian aging [20], a stronger relationship with the number of early antral follicles [10], and better cycle-to-cycle reproducibility [21] compared with FSH, E2 and inhibin B levels. Recent results show AMH to be a predictor for success rates in ART [22–24]; however, others have not found it predictive of pregnancy outcome [16, 25, 26]. Furthermore, there were few reports addressing the clinical significance of AMH levels measured at late follicular phase during ovarian stimulation. Our prospective study was designed to investigate whether AMH levels at basal and ovulation triggering day compared with FSH, LH, E2, inhibin B, and AFC are associated with ovarian response and pregnancy outcome for stimulated IVF cycles.

Materials and methods

Subjects

A total of 60 infertility women enrolled in our IVF program were recruited for the prospective study between January 2007 and December 2007. The inclusion criteria were: (1) first cycle of ovarian stimulation, (2) <40 years of age, (3) both ovaries present on transvaginal ultrasound scan, (4) no previous history of ovarian surgery, and (5) no evidence of endocrinological disorders (normal testosterone, prolactin, thyroid stimulating hormone), (6) absence of any hormonal therapy in the past 3 months.

The study was approved by the Institutional Review Board (IRB) and the committee on ethics for research involving human subjects of Changhua Christian Hospital Medical Center (Republic of China). All couples participating in the study signed informed consent.

Blood sampling and hormones assays

On day 3 (D3) of the menstrual cycle before treatment, blood samples for assay of FSH, inhibin B, AMH, luteinizing hormone (LH) and estradiol (E2) were collected, about 5 ml, by venipuncture and divided into 2 plain tubes. All samples were immediately centrifuged to separate the serum and stored in aliquots at −70°C. One tube was used for the FSH, LH, and E2 assays, and the other was for inhibin B and AMH. AMH was measured by using the ultrasensitive ELISA (Bechman-Caulter, France) and inhibin B was measured by a double antibody ELISA (Serotec, Varilhes, France). All samples were assayed at the same time to minimize intra-assay variation. Serum levels of FSH, LH and E2 were determined by using RIA kit.

Another blood samples on the day of administration of hCG (DhCG) were also collected and measured in the same way.

Stimulation protocol

Before starting treatment, the total number of antral follicles measuring 2–10 mm in diameter was counted by transvaginal ultrasound. All patients underwent IVF treatment using GnRH antagonist protocol and the COH protocol was as previously described [27]. In brief, ovarian stimulation was initiated with exogenous gonadotropins in the form of recombinant FSH (Gonal-F, Serono) from day 3 of cycle. The starting daily dose was decided according to the age and the baseline FSH levels. GnRH antagonist (cetrorelix, Serono) 0.25 mg subcutaneous injection daily was given since day 8 of cycle for preventing premature LH surge. On the same day, a changing dosage of gonadotropin was given according to sequential transvaginal ultrasonography and serum E2. When at least two or more follicles of ≥18 mm in diameter were detected; hCG (5,000 IU, Pregnyl, Organon) was administered. Transvaginal ultrasound-guided oocyte retrieval was performed 36 h after hCG injection. The number of retrieval oocytes was recorded. The oocytes were then fertilized in the laboratory with her partner's sperm. Fertilization was assessed using an established pronuclei scoring system. Then embryos were transferred 2 days later and vaginal progesterone gels (crinone 90 mg daily) were used to support luteal phase till the day of serum pregnancy test. The number of transferred embryo was decided to the wish of the couple and the number of embryos available. A positive pregnancy test was defined by >50 IU/L of plasma β-hCG on day 14 after embryo transfer. Two weeks later, a transvaginal ultrasound was done to confirm a clinical pregnancy.

The study group was divided into two subgroups according to the number of oocytes retrieved. Patients with an oocyte count of four or less were considered poor responders, and patients with more than four as normal responders.

Statistical analysis

All analyses were performed using SPSS software version 15.0 (SPSS Inc., Chicago, IL). Fisher's exact test was used to examine differences with categorical variables. Values are presented as mean (±SD). We used Mann-Whitney *U* test, Kruskal Wallis test and Jonckheere-Terpstra test to compare the different groups. Pearson (r) correlation coefficients were calculated to explore the relationships between the measured parameters. Multivariate logistic regression analyses were used to test the association

between poor response (oocyte No.≦ 4) or pregnancy with the measured parameters. For all statistical analyses, $P<0.05$ was considered to be statistically significant.

Results

Of the 60 women tested, 14 had ≦ 4 oocytes (poor responders), and 46 had ≧ 5 oocytes (normal responders). Table 1 shows patient and ovarian reserve test characteristics of poor and normal responders. Statistically significant differences existed between poor and normal responders in D3 FSH, LH, inhibin B, AFC, and AMH levels The main parameter of the study, D3 AMH, was found to be considerably higher in normal responders; mean level was 4.4±2.2 ng/mL. The AMH level was 0.7±0.8 ng/mL in poor responders ($P<0.01$)

There were statistically significant positive correlations between the number of retrieved oocytes and D3 AMH ($r=0.885$, $P<0.001$), followed by AFC ($r=0.874$, $P<0.001$), DhCG AMH ($r=0.742$, $P<0.001$), and DhCG inhibin B ($r=0.730$, $P<0.001$) (Table 2). Statistically significant inverse correlations between the number of retrieved oocytes and D3 FSH ($r=-0.521$, $P<0.001$), and age ($r=-0.385$, $P=0.002$) were also observed. No correlation was identified between the number of retrieved oocytes and D3 inhibin B ($P=0.776$) or LH ($P=0.616$). Overall, D3 AMH had the strongest statistically significant correlation with the number of oocytes that were retrieved. D3 AMH levels were correlated with AFC ($r=0.836$; $P<0.001$).

The clinical pregnancy rate per started cycle was 43.3% (26/60). Data for pregnant and nonpregnant women are presented in Table 3. D3 AMH and AFC were significantly different between pregnant and nonpregnant women.

Table 1 Patient and ovarian reserve test characteristics in the poor and normal-responder groups

Variable	Poor responder	Normal responder	P
Age(y)	33.8±3.6	30.0±3.1	0.06
BMI(kg/m^2)	23.1±0.9	21.2±0.5	0.322
No. of oocytes	4.0±0.9	9.0±4.1	0.01
Fertilization(%)	75.0±17.7	59.2±15.6	0.455
D3 FSH (IU/L)	8.0±1.4	5.4±1.1	0.01
D3 LH (IU/L)	3.3±0.5	4.3±0.8	0.03
Antral follicle count	6.0±1.3	10.0±4.3	0.01
D3 AMH (ng/mL)	0.7±0.8	4.4±2.2	0.01
DhCG AMH (ng/mL)	0.6±0.7	3.1±1.7	0.01
D3 inhibin B (ng/mL)	51.1±86.4	79.3±63.0	0.02
DhCG inhibin B (ng/mL)	286.7±294.6	854.6±497.5	0.01
D3 estradiol (pg/mL)	32.8±16.8	30.7±14.8	0.793

Table 2 Correlation coefficients between the number of oocytes collected and the parameters investigated

Variable	r	P
D3 AMH (ng/mL)	0.885	<0.001
Antral follicle count	0.874	<0.001
DhCG AMH (ng/mL)	0.742	<0.001
DhCG inhibin B (ng/mL)	0.730	<0.001
D3 FSH (IU/L)	−0.521	<0.001
Age (y)	−0.385	0.002
D3 LH (IU/L)	0.066	0.616
D3 inhibin B (ng/mL)	0.038	0.776

Women who achieved pregnancy had higher AMH levels (4.3±2.6 ng/mL vs. 3.4±2.4 ng/mL; $P=0.011$), but similar FSH levels (5.6±1.2 IU/L vs. 6.0±1.7 IU/L; $P=0.31$).When multiple regression analysis was used for prediction of clinical pregnancy, D3 AMH levels were the only independent predictors of pregnancy (β coefficient [±SE], 0.635± 0.325; $P=0.049$) (Table 4). Neither AFC nor D3 FSH proved to be an independent predictor.

Discussion

This prospective study was conducted to evaluate the relevance of routine AMH measurements during IVF treatment. Age, FSH-, inhibin B- and AMH-levels and their predictive values for ovarian response and clinical pregnancy rate were compared by discriminant analyses.

Currently, most IVF clinicians determine starting doses of gonadotrophin in the first cycle of IVF based principally on age and basal FSH levels [28]. Our study suggests that AMH and AFC are superior predictors of oocyte yield compared with age and basal FSH. Linear regression analysis shows a significant association between AMH,

Table 3 Characteristics of pregnant and nonpregnant women

Variable	Nonpregnant (n=34)	Pregnant (n=26)	P
Age (y)	31.5±4.4	32.0±2.9	0.822
BMI (kg/m^2)	22.9±0.7	21.7±0.5	0.41
No. of oocytes	7.0±4.1	8.5±4.9	0.051
D3 FSH (IU/L)	6.0±1.7	5.6±1.2	0.310
D3 LH (IU/L)	3.9±1.2	4.3±1.1	0.53
AFC	9.0±3.7	11.0±5.3	0.007
D3 AMH (ng/mL)	3.4±2.4	4.3±2.6	0.011
DhCG AMH (ng/mL)	2.4±1.7	2.6±1.9	0.170
D3 inhibin B (ng/mL)	66.3±79.8	77.4±54.1	0.420
DhCG inhibin B (ng/mL)	736.2±497.6	823.0±523.2	0.052

Table 4 Multivariate logistic regression analysis of factors predictive of clinical pregnancy

Variable	β	SE	Odds ratio 95% C.I.		*P*-value
AFC	0.055	0.122	1.057	0.833−1.341	0.649
D3 AMH	0.635	0.325	1.887	1.297−3.570	0.049
DhCG AMH	−0.603	0.347	0.547	0.277−1.081	0.083
D3 FSH	0.062	0.253	1.064	0.648−1.746	0.807
D3 LH	0.011	0.022	1.011	0.968−1.056	0.609
D3 inhibinB	−0.002	0.005	0.998	0.989−1.007	0.705

AFC, and FSH and the number of oocytes collected. In keeping with the recent study [29], AMH correlates better than age, FSH, LH, E2, and inhibin B with the number of retrieved oocytes. Our analysis confirmed that AMH and baseline FSH demonstrate a negative linear relationship and that, as previously noted [30]. Consistent with previous studies [8, 10, 13, 16, 23, 31], our results demonstrated a strong association among AMH and antral follicles and retrieved oocyte count. The performance of AMH in the prediction of poor response from the other studies and the correlation between AMH and retrieved oocyte count, are summarized in Table 5.

Therefore, serum basal AMH levels may reflect the size of antral follicle pool and provide a marker associated with the number of retrieved oocytes after controlled ovarian hyperstimulation (COH). Furthermore, our findings are in agreement with those of the previous studies [32, 33] in that serum AMH at ovulation triggering day has a significant positive correlation with the number of oocytes retrieved.

We observe that D3 AMH levels and AFC were significantly lower in the poor responders than in the normal responding women (Table 1). The performance of AMH in identifying poor responders was very similar to that of AFC in the previous studies [13, 16, 34]. However, an accurate AFC depends on the clinician's experience and the ultrasound properties. By contrast, AMH levels are obtained by objective measurements performed in laboratory medium and thus are free of interobserver variability and personal comments.

In agreement with other studies [11, 35–37], we found that serum AMH level declined significantly during COH , thus confirming the reported low levels of AMH expression by larger follicles. Although the physiological mechanisms implicated in such a process remain undetermined, these results are in keeping with previous study indicating that AMH is preferentially secreted by pre-antral and early antral follicles [18]. This decrease in AMH concentrations between start of stimulation and the day of hCG administration reflects the reduction in the number of small growing follicles recruited during ovarian stimulation [11, 35].

One of most attractive advantages of AMH is that its levels have been shown to be stable under various influences such as hormonal contraception [38, 39], GnRH agonist [40], pregnancy [41], and the menstrual cycle [42–45]. Therefore, measurements can be made anytime during the menstrual cycle. However, two reports suggested that AMH levels actually fluctuate during the menstrual cycle [46, 47]. Discrepancies between studies might be explained by differences in age of population, size of population, and methodology of the AMH assay. Two commercial AMH ELISA assays (Beckman Coulter and DSL) are available on the market. A recent study showed a close linear relationship between the two methods but the AMH levels were almost 4.6-fold higher with the Beckman Coulter than with the DSL kit [48]. Recently, Streuli et al [49] concluded that the changes in AMH levels after ovulation are slight, and therefore are not clinically relevant as far as AMH measurements for clinical purposes are concerned. In daily

Table 5 Performance of anti-Müllerian hormone (AMH) in the prediction of poor response in IVF patients and the correlation between AMH and retrieved oocyte count

Author	Cycles (n)	AMH cut-off value	Sens (%)	Spec (%)	r
Van Rooij 2002 [10]	119	0.3 μg/L	60	89	0.57
Eldar-Geva 2005 [13]	69	0.1 ng/mL	76	88	0.647
Muttukrishna 2005 [8]	108	0.2 ng/mL	87	64	0.51
Penarrubia 2005 [14]	80	4.9 pmol/l	40	92	NA
Ebner 2006 [58]	141	1.66 ng/mL	69	86	NA
Ficicioglu 2006 [16]	44	0.25 pg/mL	91	91	0.564
La Marca 2006 [43]	48	0.5 ng/mL	85	82	0.73
McIlveen 2007 [52]	84	1.25 ng/mL	58	75	NA
Smeenk 2007 [25]	80	1.4 μg/L	62	73	NA
Wunder 2008 [23]	276	NA	NA	NA	0.357
Barad 2008 [24]	76	0.5 ng/mL	87	84	NA
Riggs 2008 [29]	123	0.83 ng/mL	83	79	0.539
Nardo 2008 [31]	165	1.0 ng/mL	97	41	NA
Gnoth 2008 [53]	132	1.26 ng/mL	97	41	NA

r: Pearson's correlation between AMH and retrieved oocyte count, $P<0.01$

Sens=Sensitivity; Spec=specificity; NA=Not available

practice, AMH therefore can be measured anytime during the menstrual cycle.

Predicting the ovarian reserve in IVF patients is useful in optimizing the stimulation protocol to obtain a good response. However, it remains a challenge to identify young women, with normal ovulatory cycles but low ovarian reserve. Compared to inhibin B and AFC, AMH was more consistently correlated with the clinical degree of follicle pool depletion in young women presenting with elevated FSH levels [50]. A younger woman with a reduced ovarian reserve may then choose to pursue treatment sooner. A further potential application for the prediction of poor response is the augmentation of the starting dose of gonadotrophins in predicted poor responders. It is not certain that this may lead to higher pregnancy rates [51], but randomized prospective data on this issue are still lacking.

Application of AMH, as a predictor of ongoing pregnancy following IVF appears to be limited in view of the fact that they only represent the quantitative aspect of ovarian reserve, whereas pregnancy is also dependent on the oocyte quality, embryo development and endometrium receptivity. Therefore, some studies had shown that the serum level of AMH found to predict oocyte number may not predict the probability of pregnancy [14, 16, 25, 26, 52–55]. However, we found that high serum AMH levels correlated not only with oocyte number but also with pregnancy rates. D3 AMH and AFC were significantly different between pregnant and non-pregnant women (Table 3). When logistic regression analysis was used for prediction of clinical pregnancy, D3 AMH levels were the only independent predictors of pregnancy. Neither AFC nor D3 FSH proved to be an independent predictor. While our results show such an association, the number of pregnant women is very small to make such a correlation. A recent meta-analysis study examining the link between AFC and pregnancy outcome found that AFC was not predictive of pregnancy during IVF treatment [56]. Another recent study also found that AMH was superior in predicting IVF outcomes in comparison with FSH [24]. Moreover, recent reports suggested better predictive capabilities for pregnancy for AMH [12, 13, 22–24, 57]. These results confirm those found by other investigators, whose studies showed that serum AMH levels during COH may reflect oocyte and embryo quality [31, 58]. Up to now, only one study has been published relating serum AMH levels to the live birth rate following IVF [59]. In this prospective study, it was demonstrated that the live birth rate dramatically increases with increasing basal AMH value.

Recently, a large prospective study performed on 538 patients undergoing ART [60], indicates that a single AMH assay may be used to individualize treatment strategies for IVF. The AMH-based strategy of controlled ovarian stimulation was associated with a significant reduction of excess response to stimulation, reduced cycle cancellation and a trend towards increased clinical efficacy. Although AMH has the potential to guide clinical management in IVF, a number of important questions relating to its clinical implications need to be answered [61].

In conclusion, there are many advantages of using serum AMH over other serum markers. Firstly, serum AMH levels begin to decline before serum FSH and inhinbin B levels become abnormal [20]. Secondly, serum AMH can be measured throughout the cycle, in contrast to the other parameters, which can only be determined in the early follicular phase. Finally, unlike AFC measurements, serum AMH assays are not observer-dependant, resulting in less interobserver variability. In this preliminary study, we found that either ultrasonic (AFC) or endocrine assessment (basal AMH and FSH) could predict ovarian response. Our results may support the assumption that there is an association between AMH and pregnancy rate in IVF based on the small sample size. This issue requires to increase the numbers of subjects in an effort to increase the power of the study.

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