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ASSISTED REPRODUCTION TECHNOLOGIES

Serum anti-Müllerian hormone and antral follicle count as predictive markers of OHSS in ART cycles

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Abstract
Objective To evaluate predictive role of day–3 serum anti-Müllerian hormone (AMH) levels and antral follicle count (AFC) in ovarian hyperstimulation syndrome (OHSS) in patients undergoing IVF/ICSI cycles.
Materials and methods Forty-one women with moderate/severe OHSS and 41 age matched women without OHSS were compared to evaluate the predictive value of certain risk factors for OHSS. AFC, and E_2, FSH, LH, AMH, inhibin-B levels measured on day 3 of the menstrual cycle before controlled ovarian hyperstimulation.
Results Mean FSH was significantly lower ($p<0.0001$); and mean LH, AFC and AMH were significantly higher in women with OHSS compared to women without OHSS ($p=0.049$, $p<0.0001$ and $p<0.0001$, respectively). There was no significant difference in inhibin B ($p=0.112$) and estradiol ($p=0.706$) between the groups. The ROC area under curve (AUC) for AMH presented the largest AUC among the listed risk factors. AMH (AUC=0.87) and AFC (AUC=0.74) had moderate accuracy for predicting OHSS while Inhibin B (AUC=0.58) and LH (AUC=0.61) had low accuracy. The cut-off value for AMH 3.3 ng/mL provided the highest sensitivity (90%) and specificity (71%) for predicting OHSS. It's positive (PPV) and negative predictive values (NPV) were 61% and 94%, respectively. The cut-off value for AFC was 8 with 78% sensitivity, 65% specificity, 52% PPV and 86% NPV.
Conclusion Measurement of basal serum AMH and AFC can be used to determine the women with high risk for OHSS.

Keywords Antimullerian hormone · Ovarian hyperstimulation syndrome · Antral follicle count

Capsule Day–3 serum anti-Müllerian hormone (AMH) levels and antral follicle count (AFC) can predict ovarian hyperstimulation syndrome (OHSS) in patients undergoing IVF/ICSI cycles.

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is a severe complication observed in some patients undergoing controlled ovarian hyperstimulation (COH) during in vitro fertilization (IVF) [1]. OHSS is characterized by an increase in ovarian size associated with a dramatic increase in vascular permeability causing ascites and eventually amore severe and possibly lethal form of infertility requiring hospitalization in otherwise healthy women [2].

The specific risk factors for OHSS include young age, lean habitus, polycystic ovarian syndrome (PCOS), the presence of multiple small and intermediate follicles, and excessively high levels of serum estradiol (E_2) on the day of HCG (>4,000 pg/mL) [3–5]. However, prediction of OHSS prior to COH in an individual IVF cycle using only age and body mass index (BMI) remains a difficult task [6]. Monitoring the serum E_2 level and number of follicles has been effective in reducing the incidence of OHSS, but these are determined near the completion of COH [7, 8].

If it would be possible to accurately predict OHSS before starting ART cycle, a better alternative would be chosen for COH with lesser risks for the patients, such as using GnRH antagonists for pituitary suppression and GnRH agonists to trigger oocyte maturation. Therefore fewer cycles would be canceled.

Recently, serum anti-müllerian hormone (AMH) levels have been reported to better reflect the level of ovarian reserve than other markers such as basal serum FSH, inhibin B levels and antral follicle count (AFC). OHSS has been reported to be associated with high serum levels of AMH prior to COH. Patients with cancelled cycles due to a high risk of OHSS had serum AMH levels in the highest quartile, and basal serum AMH levels could be utilized effectively to predict OHSS [9–13].

The aim of this study was to determine the value of serum AMH levels and AFC as predictors of OHSS in patients undergoing a first cycle of COH for IVF/ICSI cycles.

Material and methods

Subjects

Patients undergoing IVF/ICSI cycles in Istanbul University, Cerrahpasa School of Medicine, Department of Obstetrics and Gynecology, IVF Unit between January 2008 and January 2010 were retrospectively reviewed to evaluate the predictive value of certain risk factors including age, body mass index (BMI), AFC, and E_2, FSH, LH, AMH, and inhibin B levels measured on day 3 of the menstrual cycle for OHSS before COH. During this period 695 patients were treated by IVF/ICSI and 41 of 695 women had moderate or severe OHSS at their first cycle. This study group was compared to 41 age matched women who were at their first cycle and did not have OHSS.

Criteria for inclusion were a written informed consent for the IVF/ICSI treatment, a patient age of 40 maximum, a basal FSH (day 3) level of <15 mIU/mL, body mass index of 18–30 kg/m^2; normal prolactin and thyroid stimulating hormone (TSH) values, normal gynecological ultrasound, and cervical smear. Exclusion criteria for an IVF/ICSI treatment were acute infectious diseases, systemic illnesses, and known hypothalamic, pituitary and surrenal disorders. The local ethics committee approved the study.

Diagnosis of OHSS

The criteria for classification of OHSS defined by Navot et al. [3] were used to assess the relative severity of OHSS. Moderate OHSS was characterized by abdominal distension and ascites and ovarian size of 8–12 cm on ultrasonography. Severe OHSS consisted of clinical ascites with or without pleural effusion, oedema, oliguria, hematocrit levels >45%, white blood cell count >15,000/mm^3, a serum creatinine of 1.0–1.5 mg/mL, and abnormal liver function tests. Only those patients with a moderate or severe OHSS were classified as having a positive case of OHSS. Diagnosis of moderate OHSS was made by the presence of abdominal distension and ascites and ovarian size of 8–12 cm on ultrasonography. Diagnosis of severe OHSS was made by presence of one of the clinical (clinical ascites with or without pleural effusion, oedema, oliguria), or laboratory (hematocrit levels >45%, white blood cell count >15,000/mm^3, a serum creatinine of 1.0–1.5 mg/mL, and abnormal liver function tests) criteria in a patient with moderate OHSS.

Study protocol

On day 2–3 of a spontaneous cycle within 3 months of commencing ovarian stimulation, blood samples for assay of E_2, FSH, LH, AMH and inhibin B levels were obtained. All patients received GnRH agonist leuprolide acetate (1 mg/day sc Lucrin®, Abbott-France Pharmaceuticals, France) beginning on the 21st day the of previous cycle. Leuprolide acetate was reduced to 0.5 mg/day and gonadotropin 150–225 IU (Menogon®, Ferring, Istanbul; Gonal F®, Merck Serono, Istanbul; or Puregon®, Schering Plough, Istanbul) were initiated on the third day of menstruation based on age, body mass-index (BMI) and basal FSH value.

COH was monitored by transvaginal sonography, and then the dose of gonadotropin was adjusted according to the follicle size and number. When three or more follicles reached >18 mm, both the gonadotropin and agonist injections were stopped and either 10,000 IU of hCG (Pregnyl®, Schering Plough, Istanbul) or rechCG (Ovitrelle®, Merck Serono, Istanbul) was given.

Egg collection was planned 34–36 h after hCG injection, followed by embryo transfer 72 h after oocyte retrieval. Luteal phase was supported with progesterone (200 mg administered vaginally three times daily Progynex®, Koçak, Istanbul, or Crinone gel® 8%, Merck Serono, Istanbul) or by 100 mg progesterone injection IM daily (Progynex® ampoule, Koçak, Istanbul) until the day of the pregnancy test 15 days after the embryo transfer.

Hormone assays

AMH. All samples were assayed in duplicate using the AMH/MIS enzyme-linked immunosorbent assay kit (Diagnostic Systems Lab, Webster, Texas, USA). The sensitivity of the assay was 0.017 ng/mL. The intra- and inter- assay variations were <5% and <8%, respectively.

Inhibin B. All samples were assayed in duplicate using a commercial ELISA kit (Diagnostic Systems Lab, Webster,

Texas, USA). The sensitivity of the assay is 7 pg/mL. The intra- and interassay variations were <6% and <8%, respectively.

FSH, Estradiol, and LH. These were measured by Chemiluminescent Microparticle Immunoassay (Architect Abbott Lab, IL, USA).

Statistical analysis

Results were expressed as mean±SD, frequency, and percentages. One sample Kolmogorov-Smirnov test and histogram graphics were used to show the distribution. Categorical characteristics of patients were compared with $\chi 2$ test. Independent Samples *T* test and Mann Whitney U tests were used for comparison of numeric variables.

Receiver operating characteristic (ROC) curve analysis and comparison of area under curves (AUC) were performed to determine cut-off values of FSH, inhibin B, AMH, LH, age, gonadotropin dose and AFC for the prediction of OHSS and to calculate their sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the prediction of OHSS. The standard AUC definitions were as follows: AUC=1 indicates a perfect test, AUC>0.9 indicates high accuracy and AUC between 0.7 and 0.9 indicates moderate accuracy. Analyses were performed in Statistical Package for the Social Sciences (SPSS) 17.0 and Medcalc 11.4.4.0 (free trial). A p value of <0.05 was considered statistically significant.

Results

Of 695 IVF ICSI cycles, 41 (5.8%) were complicated by OHSS and among 41 cycles 11 were severe OHSS. These 41 women with moderate or severe OHSS were compared to 41 age-matched women who underwent IVF/ICSI in the same period and did not have OHSS.

Table 1 summarizes patients' demographics; mean basal E_2, FSH, LH, AMH, inhibin B levels, AFC and treatment characteristics. There was no significant difference between the two groups with regard to different gonadotropin types. Gonadotropin dose was significantly lower in women with OHSS compared to women without OHSS (1891±875 U vs. 2595±1331 U, p=0.003).

We found no significant difference between the two groups regarding mean BMI (p=0.188), day 3 E_2 (p=0.706) and inhibin B (p=0.112).

Mean FSH was significantly lower in women with OHSS compared to women without OHSS (5±1.8 vs. 6.9±3.8; p<0.0001). Mean AMH and AFC was significantly higher in women with OHSS compared to women without OHSS (6.9±3.9 vs. 2.9±2; p<0.0001 and 12.9± 6.8 vs. 8.2±6.0; p<0.0001, respectively). LH was very slightly higher in women with OHSS compared to women without OHSS (4.7±3.0 vs. 3.8±2.6, p=0.049).

Table 2 shows the results of ROC for the sensitivity, specificity, PPV, and NPV of the AMH, AFC, inhibin B and LH in predicting the risk of OHSS. The ROC area under curve (AUC) for AMH presented the largest AUC among the listed risk factors; and the AUC for AMH was significantly larger than the corresponding values for AFC, LH, and inhibin B (Fig. 1). The ROC-AUC of inhibin B, LH and FSH were non-significant (ROC-AUC: 0.58; ROC-AUC: 0.61; ROC AUC: 0.34; respectively).

The ROC-AUC for AMH was 0.87 with a 95% CI (0.80–0.92). The cut-off value for AMH 3.3 ng/mL was determined with the highest sensitivity (90%) and specificity (71%) for predicting OHSS and its PPV and NPV were 61% and 94%, respectively. Comparison of sensitivity, specificity, NPV, and PPV of different AMH threshold values for prediction of OHSS are presented in Table 3.

The ROC-AUC for AFC was 0.74 with a 95% CI (0.66–0.82). The cut-off value for AFC 8 was determined with the

Table 1 Patients' demographics, mean basal E_2, FSH, LH, AMH, inhibin B levels, AFC and treatment characteristics

	OHSS present (n=41)	OHSS absent (n=41)	P value
Age (year) mean±SD	29.3±4.6	29.3±4.6	1.000
BMI (kg/m^2) mean±SD	24.4±4.2	25.0±3.9	0.188[a]
Gonadotropin dose (U) mean±SD	1891±875	2595±1331	0.003[a]
Gonadotropin type n(%)			
HMG	15 (37%)	16 (39%)	0.153[c]
recFSH	26 (63%)	25 (61%)	
AMH (ng/mL) mean±SD;	6.9±3.9	2.9±2.0	<0.0001[b]
FSH (mIU/mL) mean±SD;	5.0±1.8	6.9±3.8	<0.0001[b]
LH (mIU/mL) mean±SD;)	4.7±3.0	3.8±2.6	0.049[b]
Inhibin B (pg/mL) mean±SD	97.9±60.8	80.7±51.5	0.112[a]
E_2 (pg/mL) mean±SD;	41.8±29.4	43.6±22.9	0.706[b]
AFC mean±SD;	12.9±6.8	8.2±6.0	<0.0001[b]
Number of pregnancies n(%)	15 (37.5%)	18 (43%)	0.77[c]

AMH anti-müllerian hormone; *BMI* body-mass index; *E_2* Estradiol; *FSH* follicle stimulating hormone; *GnRH* gonadotropin releasing hormone; *HMG* human menopausal gonadotropin; *LH* luteinizing hormone. *NS* non-significant

[a]Independent samples t test (2 tailed),

[b]Mann Whitney *U* test,

[c]Chi square test

Table 2 Comparison of ROC-AUC, sensitivity, specificity, NPV, and PPV of various markers for prediction of OHSS

	AUC (95% CI)	cut-off value	Sensitivity (95% CI)	Specificity (95% CI)	NPV	PPV
AMH	0.87 (0.80–0.92)	3.3	0.90 (0.77–0.97)	0.71 (0.61–0.81)	0.94 (0.84–0.98)	0.61 (0.47–0.73)
AFC	0.74 (0.66–0.82)	8	0.78 (0.62–0.89)	0.65 (0.54–0.76)	0.86 (0.74–0.93)	0.52 (0.39–0.65)
Inhibin B	0.58 (0.49–0.67)	83.5	0.57 (0.40–0.72)	0.58 (0.47–0.69)	0.75 (0.63–0.85)	0.38 (0.25–0.51)
LH	0.61 (0.52–0.69)	4.2	0.54 (0.37–0.69)	0.75 (0.64–0.84)	0.77 (0.66–0.85)	0.51 (0.36–0.66)
FSH	0.34 (0.23–0.44)	5.17	0.51 (0.32–0.55)	0.67 (0.54–0.71)	0.68 (0.61–0.74)	0.48 (0.30–0.57)

AMH antimullerian hormone; *AFC* antral follicle count; LH, luteinizing hormone; *ROC-AUC* Receiver Operating Characteristic - Area Under Curve; *NPV* negative predictive value; *PPV* positive predictive value; *FSH* follicle stimulating hormone

highest sensitivity (78%) and specificity (65%) for predicting OHSS and its PPV and NPV were 52% and 86%, respectively.

According to the standard definitions of AUC, AMH (AUC=0.87) and AFC (AUC=0.74) had moderate accuracy for predicting OHSS while Inhibin B (AUC=0.58) and LH (AUC=0.61) had low accuracy.

Discussion

This study showed that 5.8% of 695 IVF ICSI cycles were complicated by moderate or severe OHSS; 1.5% of those were severe OHSS. These findings are in keeping with the incidence of OHSS (5–9%) that has been reported in the literature; and the severe form of the syndrome may occur in 1–3% [14].

Since the exact pathogenesis of OHSS is poorly understood, its prediction is difficult. OHSS has clear risk factors such as polycystic ovaries, young age, lean habitus, a high number of antral follicles, high E_2 on the day of hCG and previous OHSS [15, 16]. But OHSS can occur in the absence of currently recognized risk factors. In our study the mean BMI of the two groups were not different.

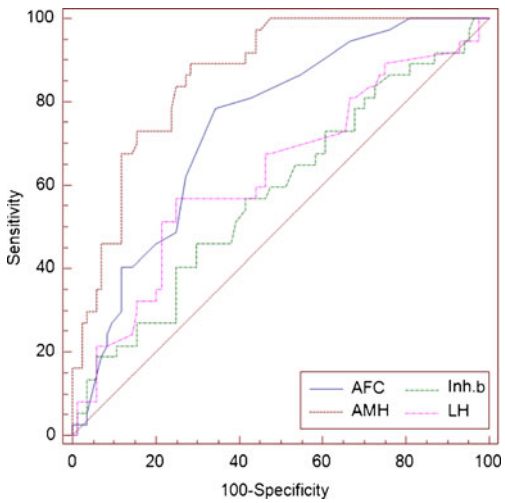

Fig. 1 The ROC area under curves for prediction of OHSS

The key to prevent OHSS is the recognition of risk factors leading to an individualization of gonadotropin starting dose which should be the minimum dose necessary to achieve the therapeutical goal or usage of a GnRH antagonist for pituitary suppression and an agonist to trigger oocyte maturation. However, accurate prediction of OHSS in an individual IVF cycle is difficult.

AMH is produced by the granulosa cells of primary and preantral follicles, [17, 18] and is a member of the transforming growth factor-ß family synthesized exclusively by the gonads of both sexes. Over the last decade, several studies have examined the clinical usefulness of serum AMH levels as a predictor of ovarian response and pregnancy in ART cycles [12]. The recognition of a dose–response relationship between AMH and ovarian response to FSH leads to the hypothesis that hyperresponse to ovulation induction might result from high AMH. In this context high basal AMH may be associated with an increased risk of developing OHSS. Lee [19] and Nardo [20] have independently calculated a similar performance of AMH for the prediction of hyper response and OHSS.

In the present study we used a cut-off level of day 3 AMH >3.3 ng/mL to determine the risk of OHSS with 90% sensitivity, 71% specificity, 61% PPV, and 94% NPV. We found that AMH is a better predictor than AFC, LH, inhibin B and FSH.

To evaluate the predictive value for OHSS by means of age, BMI, estradiol and AMH levels, a cohort of 262 IVF cycles was investigated by Lee et al. [19], and they found that the ROC of the basal AMH was larger than age and BMI, and works equally well as the number of follicles and estradiol levels on the day of hCG. Basal AMH levels predicted OHSS with a sensitivity of 90.5% and specificity of 81.3%. Interestingly, the cut-off value calculated (3.36 ng/ml) corresponded to the highest quartile (75–100%) of the AMH values in their population, suggesting that hyperresponse and OHSS may be caused by gonadotropin administration to women with enhanced ovarian

Table 3 Comparison of sensitivity, specificity, NPV, and PPV of different AMH threshold values for prediction of OHSS

Cut-off value	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
2.29 ng/ml	100% (91.4–100)	52.3% (41.2–63.4)	100 (92–100)	50.6 (39.2–62)
2.53 ng/ml	92.6% (80.1–98.5)	57.1% (45.9–67.9)	94.1 (83.6–98.8)	51.4 (39.3–63.3)
3.3 ng/ml	90% (0.77–0.97)	71% (0.61–0.81)	94 (0.84–0.98)	61 (0.47–0.73)
3.88 ng/ml	75.6% (59.7–87.6)	78.5% (68.3–86.8)	86.8 (77.1–93.5)	63.3 (48.3–76.6)
4.3 ng/ml	75.6% (59.7–87.6)	82.1% (72.3–89.6)	87.3 (77.9–93.8)	67.4 (52–80.5)
5.07 ng/ml	56.1% (39.7–71.5)	88.1% (79.2–94.1)	80.4 (70.9–88.0)	69.7 (51.3–84.4)
10.2 ng/ml	17% (7.2–32.1)	100% (95.7–100)	71.2 (62.1–79.2)	100 (59.0–100)

AMH antimullerian hormone; *NPV* negative predictive value; *PPV* positive predictive value; *OHSS* ovarian hyperstimulation syndrome

reserve. In the study of Lee, AMH-AUC for OHSS was 0.902 which is very close to the value (AUC=0.87) found in our study. In Lee's study OHSS rate was 8% (21/262) and 19 of 21 OHSS cases were found in 75–100% group. In this group mean BMI was lower compared to our study group (21.2±0.4 vs. 24.4±4.2); this may be a possible explanation for the high OHSS rate, since OHSS is more frequent in lean patients. [3] In Lee's study, the mean serum AMH level for OHSS patients was significantly higher compared to mean serum AMH level of OHSS patients in our study (n=21, 5.02 ng/ml vs. n=41, 6.9 ng/ml, respectively, p<0.0001); although the same kit was used in both studies. This difference could be attributed to individual characteristics of patients in two groups.

Broer et al. [21] performed a meta-analysis of 9 studies reporting on predictive value of AMH for OHSS and they found that summary estimates of sensitivity and specificity for AMH were 82 and 76%, respectively. In our study, the sensitivity and specificity of AMH were 90% and 71%, respectively. Broer et al. also evaluated 5 studies reporting on predictive value of AFC for OHSS and they found that summary estimates of sensitivity and specificity for AFC were 82 and 80%, respectively. In our study, the sensitivity and specificity of AFC for prediction of OHSS were 78% and 65%, respectively. Broer et al. [21] concluded that the comparison of the summary estimates and ROC curves for AMH and AFC showed no statistical difference. However in our study, AUC of AMH was significantly larger than AUC of AFC (AMH-AUC=0.87, standard error=0.0310 vs. AFC-AUC=0.74, standard error=0.0451, p=0.0175).

Considering that PCOS has been associated with high AMH levels, it is logical to conclude that the prevalence of PCOS patients among women with AMH levels in the highest AMH quartile may be increased, thus in part explaining the observed high rate of OHSS in this group of women.

But PCOS is present only in 20% of women undergoing COH and in <20% of patients developing symptoms of impending OHSS, then taking only PCOS like a predictive factor for OHSS is not sufficient [22, 23]. In our study 8.8% of women had ovulatory dysfunction.

Daninger [24] found a significant correlation between baseline ovarian volume and development of OHSS in 101 patients who underwent IVF. In their study, a significant correlation with the baseline number of follicles and development of this syndrome was also found. Other investigators have demonstrated the usefulness of ovarian volume and AFC [25, 26]. On the other hand AFC necessitates skilled ultrasound operators who carefully identify measure, and count ovarian follicles. Also there is a moderate intercycle and interobserver variability in AFC [27].

Unlike AFC measurements, serum AMH assays are not observer-dependent, resulting in less interobserver variability; it may also represent a more sensitive marker of ovarian reserve than AFC. In our study, AFC with a cut off level of 8 can predict OHSS with 78% sensitivity and 65% specificity and its PPV and NPV were 52% and 86%, respectively.

Multiple studies have suggested that early follicular phase serum AMH levels reflected the recruitable pool of antral follicles and serve as a sensitive marker of ovarian reserve. Response to ovarian hyperstimulation will be directly linked to this cohort size [28].

After evaluating several predictive criteria for OHSS, Delvigne has concluded that there were a number of factors including E_2 level and the number of follicles [4]. Morris measured E_2 levels as a predictive factor and found that all OHSS patients had high E_2 levels, but this was not accurate enough to be a predictive factor [29]. We demonstrated availability of a predictive serum marker like AMH that could potentially improve identification of patients at high risk for OHSS and allow us to minimize the incidence of this complication.

Enskog [30] observed a higher inhibin B concentration in OHSS group during the gonadotropin stimulation and

also at the day of oocyte retrieval; but only inhibin A was significantly elevated after OHSS onset while inhibin B increased gradually following FSH stimulation and was declining at the time of the LH surge. In the present study, in accord with the results of Moos [31], we found that serum concentration of inhibin B was not found to be a strong predictive factor of OHSS.

In conclusion we found that AMH (AUC=0.87) and AFC (AUC=0.74) had moderate accuracy for predicting OHSS while inhibin B (AUC=0.58) and LH (AUC=0.61) had low accuracy. A cut-off level of AMH >3.3 ng/mL determines the risk of OHSS at the beginning of COH with 90% sensitivity, 71% specificity, 61% PPV, and 94% NPV. And a cut-off value of AFC >8 in predict OHSS with 78% sensitivity and 65% specificity, 52% PPV, and 86% NPV. AMH measurement and AFC prior to COH can provide useful information to direct the application of mild patient-friendly stimulation protocols in order to avoid OHSS.

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Conflict of interest None.

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