Ovarian Reserve Test with Human Menopausal Gonadotropin as a Predictor of In Vitro Fertilization Outcome

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Purpose: Our purpose was to determine prospectively, using receiver-operating characteristic (ROC) analysis, whether the ovarian reserve test with hMG could improve the predictive value of a woman's age and basal levels of follicle stimulating hormone (FSH), E₂, and inhibin or any combination of them regarding ovarian response and pregnancy rate in IVF treatment following pituitary desensitization.

Methods: The hMG test was performed within 3 months of IVF treatment in 80 women undergoing the first cycle of IVF and consisted of 2 ampoules of hMG daily for 5 days starting on cycle days 2 to 3. Hormone and ultrasound evaluation was performed on cycle days 2 to 3 and 7 to 8.

Results: The mean age and basal FSH levels were significantly higher in the canceled ($n = 28$) than in the control ($n = 52$) group, whereas the basal inhibin level was significantly higher in the latter. Regarding ovarian response, the combination FSH plus inhibin had the better diagnostic accuracy (predictive value of 70%) among basal variables. When post-hMG parameters (alone or in combination) were analyzed, E₂ alone, with a 77% diagnostic accuracy, emerged as the best predictive variable of cancellation in IVF cycles. When ROC analysis was used, the area under the ROC curve for E₂ post-hMG (diagnostic accuracy of 84.5%) was significantly higher than that for the estimates based on the combination of basal FSH and inhibin (diag-

nostic accuracy of 71.3%). However, woman's age was the only variable independently associated with pregnancy rate.

Conclusions: The predictive power of the hMG test of ovarian reserve is better than that of age and basal hormone values (FSH and inhibin) and it is based mainly on the E₂ response to hMG treatment. However, given that age is the only predictor of pregnancy and considering the cost and discomfort of the hMG test, the usefulness, if any, of the test in predicting IVF performance in the daily clinical setting remains to be established.

KEY WORDS: FSH; hMG test; IVF; low responders; predictors of ovarian response.

INTRODUCTION

Recruitment and development of multiple ovarian follicles in response to gonadotropin stimulation are necessary for successful IVF-ET. The ability of the ovaries to respond to gonadotropins with adequate follicular development has been referred to as ovarian reserve. Although it declines with age, it is a biological and not just a chronological function. The most important aspect of diminished ovarian reserve is that the timing of its onset is highly variable (1).

IVF is expensive, time-consuming, and stressful for patients. Evaluations of IVF performance rarely consider canceled cycles, which usually result from an inadequate ovarian response to the stimulation treatment. The cycle cancellations further increase the cost and duration of therapy. Therefore, a major challenge to the IVF teams is to predict prospective patients who will be low responders and to appropriately counsel women who are potential candidates for IVF.

Traditional methodology used to assess ovarian reserve has consisted of baseline serum levels of hormones such as FSH, E₂, and inhibin and chronological age (2–5). There is general agreement that age is a poorer predictor than baseline hormone levels for ovar-

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ian response in IVF cycles. However, nonresponse to ovarian stimulation in normogonadotropic, normogonadal women has been reported (6). Therefore, it has been stressed that consideration of the glandular response to stimulation may be necessary for evaluation of the reserve of the endocrine organ in question (7).

Ovarian stimulation using hMG has been classically used for patient selection and screening for ovulation induction in anovulatory infertile women (8,9). The present report, where receiver-operating characteristic (ROC) analysis (10,11) was used, examines the relative value of the woman's age and basal levels of FSH, E₂, and inhibin or any combination of them, and ovarian reserve test with hMG, in predicting ovarian response and pregnancy rate in IVF treatment following pituitary desensitization.

MATERIALS AND METHODS

Patients Studied. We studied 80 patients undergoing the first cycle of IVF treatment, thus avoiding possible bias from experience with previous cycles regarding ovarian response to exogenous gonadotropin stimulation. Forty consecutive women having a basal (cycle days 2 to 3) FSH level ≥ 7 IU/L were initially selected (73% of them were over 35 years of age). This cutoff limit was based on the mean basal FSH value found in our IVF general population (12,13). The remaining 40 patients (50% of whom were aged ≤ 35 years) were selected as follows: a patient having a basal FSH < 7 IU/L and undergoing IVF treatment immediately after an IVF patient having a basal FSH ≥ 7 IU/L (i.e., the closest patient in temporal relationship to the index patient in our IVF program).

The mean age of the women was 34.0 ± 0.36 years (range, 28 to 41 years). Patient indications for IVF included the following primary diagnoses: tubal infertility (37% of patients), endometriosis (25%), unexplained infertility (23%), and male-factor infertility (15%). All patients had both ovaries, no previous ovarian surgery, and normal ovulatory function according to their regular menstrual pattern every 27–33 days, basal body temperature recording, and midluteal plasma progesterone and prolactin determinations. All women undergoing IVF at our assisted reproduction unit have blood samples drawn on days 2 to 3 of their menstrual cycles within 3 months of the IVF attempt for routine assay of basal FSH, E₂, and inhibin. At present, we are performing basal inhibin B measurements but the present study was carried out before this assay was available. Thus, inhibin values

in this report refer to immunoreactive inhibin serum concentrations, which according to a recent study represent an increase in both inhibin A and inhibin B, the latter being quantitatively higher than inhibin A during the early follicular phase (14).

hMG Test. The hMG test was performed during a menstrual cycle within 3 months of IVF treatment when routine baseline hormone evaluation was done. All women received 2 ampoules (150 IU) of hMG i.m. (Pergonal; Serono S.A., Madrid, Spain) daily between 1800 and 2000 for 5 days, commencing on days 2 to 3 of the spontaneous cycle. Ovarian response was assessed according to ultrasound examination and serum concentrations of E₂ and inhibin. Thus, in addition to the routine baseline hormone evaluation and ovarian ultrasonographic examination on cycle days 2 to 3, for the specific purpose of this study, which was approved by our department's ethics committee, each woman underwent a second blood sampling and ultrasonographic scanning the day after the last dose of hMG was given (i.e., cycle days 7 to 8).

For the analysis of the main purpose of this study we investigated the relative power of both basal and post-hMG serum FSH, E₂, and inhibin measurements, the follicular development post-hMG (number of follicles > 10 mm in diameter), and the woman's age in predicting ovarian response in an IVF cycle stimulated as described below. As a secondary end point the same variables were compared with respect to their predictive value of pregnancy after IVF treatment.

Ovarian Stimulation Protocol. Ovarian stimulation was carried out using FSH and hMG under pituitary suppression with GnRH agonists according to a protocol reported previously (15). In all women, pituitary desensitization was achieved by s.c. administration of leuprolide acetate (Procrin; Abbott Laboratories S.A., Madrid, Spain) (1 mg daily, which was reduced to 0.5 mg after ovarian arrest was confirmed) started in the midluteal phase of the previous cycle. Gonadotropin stimulation of the ovaries was started when serum E₂ levels declined to < 50 pg/ml and a vaginal ultrasonographic scan showed an absence of follicles > 10 mm in diameter. On days 1 and 2 of ovarian stimulation, 3 ampoules/day of hMG (Pergonal; Serono S.A.) was administered together with 3 ampoules of FSH (Neo-Fertinorm; Serono S.A.). On days 3 to 7 of ovarian stimulation, 2 ampoules per day of hMG was administered to each patient. From day 8 onward, hMG was administered on an individual basis according to the ovarian response. The criteria for hCG administration were the presence of two or more follicles > 18 mm in diameter, with five or more follicles measuring ≥ 14 mm in association

with a consistent rise in serum E_2 . Oocyte aspiration was performed with vaginal ultrasonography 35–36 hr after hCG administration. Two to three days after oocyte recovery two to four embryos per patient were replaced into the uterus. The luteal phase was supplemented with hCG. Pregnancy was diagnosed by increasing concentrations of β -hCG 12–13 days after embryo transfer and the subsequent demonstration of an intrauterine gestational sac by ultrasonography. The cycle was canceled when there were fewer than three follicles with a diameter >14 mm and serum E_2 levels <500 pg/ml after 8 days of gonadotropin therapy or when the requirements for hCG injection were not accomplished following 4 to 5 additional treatment days. Canceled versus punctured IVF cycles, and pregnant versus non-pregnant patients, thus constituted the study and control groups, respectively.

Hormone Analyses. Hormones were measured using commercially available kits. FSH serum levels were measured by an immunoradiometric assay (IRMA) (Immunotech International, Marseilles, France) and data are expressed in terms of IRP 78/549. The sensitivity of the assay was 0.5 IU/L and the intraassay and interassay coefficients of variation were less than 3.5 and 5.3%, respectively. E_2 levels in serum were estimated by direct radioimmunoassay (RIA) (bioMérieux, Marcy l'Etoile, France). Intraassay and interassay coefficients of variation were below 4.5 and 5.5%, respectively. Inhibin measurements were performed by an immunoenzymatic method (Medgenix Diagnostics, Brussels, Belgium) using two antibodies recognizing different epitopes on the α subunit of human inhibin. The standard was obtained from human follicular fluid,

1 U Medgenix being equivalent to 400 pg recombinant human inhibin from Genentech (San Francisco, CA) or to 143 U porcine MRC 86/690. The sensitivity of the assay was 0.3 U/ml and the intraassay and interassay coefficients of variation were 6 and 10%, respectively. The cross-reactivity with activin was $<1\%$. Ultrasonic scans were performed using a 5-mHz vaginal transducer attached to an Aloka sector scanner (Model SSD-620; Aloka Co. LTD, Tokyo).

Statistics and Probability Testing. For statistical analysis Student's *t*-test and chi-square test were used as appropriate. Arithmetic means $\pm$ SE and 95% CI constituted the descriptive analysis. Logistic regression was used to predict the chance of being a poor responder in an IVF cycle. Basal and post-hMG determinations were introduced as continuous variables (assuming proportional hazards) in the univariate and multivariate logistic regression analysis (stepwise procedure; model criteria: $P_{in} = 0.05$, $P_{out} = 0.10$). Logarithmic transformation was performed on all variables because of their nonnormal distribution. A logistic regression model was performed to assess the joint effect of variables and to estimate the sensitivity and specificity values for all possible combinations of the study variables. The discrimination attained between the two study groups (canceled and punctured IVF cycles) was evaluated by ROC analysis. Sensitivity, specificity, and area under the ROC curve (AUC^{ROC}) were obtained for each model. Ninety-five percent confidence intervals were calculated for each of the estimates. The models' area under the ROC curve were compared using the method of Hanley and McNeil (10). Areas of 1.0 and 0.5 denote no overlapping and

Table I. Patient Characteristics, Basal Hormonal Levels, Gonadotropin Treatment, and Ovarian Response in the Four Groups Studied^a

Variable	Canceled group (n = 28)	Control group (n = 52)	P	Pregnancy group (n = 13)	Nonpregnancy group (n = 67)	P
Age (yr)	35.85 $\pm$ 0.41	34.40 $\pm$ 0.41	<0.05	32.18 $\pm$ 0.58	35.36 $\pm$ 0.38	<0.001
Infertility factor [n (%)]			NS			NS
Tubal factor	11 (39)	19 (36.5)		7 (53.8)	22 (32.8)	
Endometriosis	7 (25)	13 (25)		3 (23)	17 (25.3)	
Unexplained	7 (25)	11 (21)		2 (15.3)	16 (23.8)	
Male factor	3 (11)	9 (17)		1 (7.6)	12 (17.9)	
Basal FSH (IU/L)	9.1 $\pm$ 0.67	6.2 $\pm$ 0.35	<0.01	6.5 $\pm$ 0.54	7.82 $\pm$ 0.39	NS
Basal inhibin (U/ml)	0.5 $\pm$ 0.03	0.8 $\pm$ 0.06	<0.05	0.60 $\pm$ 0.12	0.64 $\pm$ 0.27	NS
Basal E_2 (pg/ml)	52 $\pm$ 12.2	47.7 $\pm$ 5.8	NS	44.67 $\pm$ 5.1	50.1 $\pm$ 5.9	NS
Ampoules of gonadotropins (No.)	27.5 $\pm$ 1.2	28.9 $\pm$ 0.78	NS	29.3 $\pm$ 1.4	28.7 $\pm$ 0.5	NS
Days of stimulation	11.7 $\pm$ 0.4	10.8 $\pm$ 0.18	NS	11.1 $\pm$ 0.5	10.6 $\pm$ 0.23	NS
Peak E_2 levels (pg/ml)	303 $\pm$ 47	1879 $\pm$ 145	<0.001	1841 $\pm$ 175	2017 $\pm$ 224	NS
No. of follicles	1.8 $\pm$ 0.05	14.1 $\pm$ 1.7	<0.001	13.8 $\pm$ 1.1	14.6 $\pm$ 0.9	NS
No. of oocytes	—	11.53 $\pm$ 1.18	—	12.18 $\pm$ 1.72	10.88 $\pm$ 1.05	NS
No. of embryos per replacement	—	2.97 $\pm$ 0.39	—	3.09 $\pm$ 0.16	2.88 $\pm$ 0.19	NS

^a Values are means $\pm$ SE or n (%). NS, = not significant.

Table II. Logistic Regression Analysis for Age, Hormonal Parameters (Basal and Post-hMG), Follicular Response Post-hMG, and the Best Possible Combinations of Variables (Basal and Post-hMG) as Prognostic Indicators of Ovarian Response in IVF

Variable	Odds ratio	95% confidence interval	Sensitivity (%)	Specificity (%)	Diagnostic accuracy (%) ^a
Age alone	1.14	0.97 to 1.35	4	97.7	63.77
Basal FSH alone	5.34	1.25 to 22.74	28	90.9	68.12
Basal inhibin alone	0.46	0.21 to 1.02	32	81.8	66.77
Basal FSH plus inhibin			42.31	86.36	70.00
Inhibin	0.23	0.05 to 1.06			
FSH	1.27	1.05 to 1.54			
Follicular response post-hMG	0.18	0.04 to 0.75	7.63	94.59	72.0
Inhibin post-hMG	0.35	0.14 to 0.87	5.8	92.5	66.77
E ₂ post-hMG	0.10	0.03 to 0.35	64.7	82.5	77.19
Inhibin plus E ₂ plus follicular response post-hMG			3.91	98.11	73.02
Inhibin	0.24	0.10 to 0.74			
E ₂	0.10	0.14 to 0.87			
Follicular response	0.15	0.08 to 0.62			

^a Percentage correctly predicted cycle outcome.

no discrimination, respectively, between groups. Data were analyzed by STATA (Stata Corp., College Station, TX) statistical software.

RESULTS

Among 80 patients included in the present study, 52 underwent follicle puncture for oocyte aspiration and 28 had their IVF cycle canceled because of a poor follicular response. Thirteen patients (24% per puncture) became pregnant with IVF treatment. Table I shows patient characteristics, basal FSH, inhibin, and E₂, dose of gonadotropins used, and ovarian response observed in the four groups of patients studied. Mean age and basal FSH levels were significantly higher in the canceled than in the control group, whereas basal inhibin was significantly higher in the latter. Basal E₂ levels were similar in both groups of patients. There were no differences with respect to amount and duration of gonadotropin stimulation between canceled cycles and controls, but as expected, E₂ peak levels and the number of follicles recruited were significantly higher in the control group. When pregnancy and non-pregnancy groups were compared, significant differences were detected only with respect to the mean age of patients, pregnant women being younger than nonpregnant patients (Table I).

Table II shows logistic regression analysis probability estimates for age, basal and post-hMG hormonal parameters, follicular development post-hMG, and the best combinations of all variables considered (basal and post-hMG) regarding outcome of ovarian stimulation. On the basis of this study, the combination FSH

plus inhibin, with an accuracy (predictive value of ovarian response) of 70%, had the best prognostic reliability among basal variables but no significant differences were found when this combination was compared with the predictive value of FSH alone (68.1%) and inhibin alone (66.7%). When post-hMG parameters (alone or in combination) were analyzed, E₂ alone, with a 77.1% diagnostic accuracy, emerged as the best predictive variable of cancellation in IVF cycles. This figure was significantly different from those for inhibin post-hMG (66.7%) ($P < 0.05$) and follicular development post-hMG (72%) ($P < 0.05$).

To analyze further the diagnostic accuracy of basal and post-hMG variables to discriminate between canceled and punctured IVF cycles the AUC^{ROC} values determined with ROC analysis for each basal or post-hMG parameter and the best combination of them are also shown (Table III). Figure 1 shows the calculated

Table III. Diagnostic Accuracy of Different Basal and Post-hMG Variables to Discriminate Between Canceled and Punctured IVF Cycles Using ROC Plots^a

Variable	AUC ^{ROC}	95% confidence interval
Age alone	0.630 ± 0.07	0.48 to 0.77
Basal FSH alone	0.640 ± 0.07	0.50 to 0.78
Basal inhibin alone	0.602 ± 0.07	0.46 to 0.74
Basal FSH plus inhibin	0.713 ± 0.06	0.58 to 0.84
Follicular response post-hMG	0.688 ± 0.08	0.52 to 0.84
Inhibin post-hMG	0.725 ± 0.06	0.59 to 0.85
E ₂ post-hMG	0.845 ± 0.04	0.75 to 0.93
Inhibin plus E ₂ plus follicular response post-hMG	0.762 ± 0.05	0.69 to 0.87

^a Values are means ± SE.

Fig. 1. Receiver-operating characteristic (ROC) curves for E_2 post-hMG alone and for the combination of basal FSH and inhibin. The areas under the ROC curves ($\pm$ SE) were 0.845 ± 0.04 and 0.713 ± 0.06 ($P < 0.05$), respectively. The areas under the ROC curve of 1.0 and 0.5 denote no overlapping and no discrimination, respectively, between groups.

AUC^{ROC} values for the best predictive variables of cancellation, basal FSH plus inhibin, and E_2 post-hMG, respectively. The AUC^{ROC} for E_2 post-hMG was significantly higher than that for the estimates based on the combination of basal FSH and inhibin ($P < 0.05$). Using a level of estimated probability of 0.5 as a cutoff value, a sensitivity, specificity, and diagnostic accuracy of 64.7, 82.5, and 84.5%, respectively, were attained for E_2 post-hMG. The corresponding figures for basal FSH plus inhibin were 42.3, 86.3, and 71.3%, respectively (Tables II and III).

Table IV shows the diagnostic accuracy of different basal and post-hMG variables to discriminate between pregnancy and nonpregnancy IVF cycles using ROC plots. The best predictor of pregnancy according to the AUC^{ROC} was the woman's age, with 95% CI almost reaching statistical significance.

Table IV. Diagnostic Accuracy of Different Basal and Post-hMG Variables to Discriminate Between Pregnancy and Nonpregnancy IVF Cycles using ROC Plots^a

Variable	AUC^{ROC}	95% confidence interval
Age alone	0.688 ± 0.09	0.49 to 0.88
Basal FSH alone	0.516 ± 0.10	0.31 to 0.71
Basal inhibin alone	0.50 ± 0.09	0.30 to 0.69
Follicular response post-hMG	0.5 ± 0.11	0.26 to 0.73
Inhibin post-hMG	0.548 ± 0.1	0.33 to 0.76
E_2 post-hMG	0.5 ± 0.10	0.29 to 0.70

^a Values are means $\pm$ SE.

DISCUSSION

IVF has evolved into an important and efficient method of treating infertility, and more than 250,000 IVF cycles are performed each year all over the world (16). Since pregnancy rates in IVF cycles are related to the number of embryos transferred to patients, IVF implies the pharmacological induction of multiple follicular selection. Therefore, identification of women unable to develop multiple follicles in response to controlled ovarian hyperstimulation with gonadotropins is a major aspect for appropriate patient selection and screening for IVF (17).

The absolute number and functional capacity of follicles and germ cells comprise what is termed ovarian reserve or ovarian age, which affects a given patient's response to stimulation and her chance for success. The most important aspect of the diminished ovarian reserve and the associated decline in reproductive potential is that its onset is highly variable (1). This means that functional ovarian age, as reflected by basal FSH levels, can be discordant with chronological age. Indeed, previous reports by us and others have shown that age is a poorer predictor than pretreatment basal FSH for ovarian response in IVF cycles stimulated with gonadotropins (2–5). Similarly, we reported previously that basal inhibin is a better predictor of cancellation than age in IVF cycles, although the predictive value of ovarian response for basal inhibin was similar to that for basal FSH (diagnostic accuracy of 70%) and any two or all of the three variables studied (age,

basal FSH, and inhibin) did not improve the predictive value of FSH or inhibin alone (5). This is in agreement with results reported in the present study. It should be noted, however, that both in our previous report (5) and in the present study, immunoreactive α -inhibin was measured. Recently developed two-site enzyme-linked immunosorbent assays using specific antibodies directed against the β_A and β_B inhibin subunits have allowed the measurement of the two biologically active forms of inhibin, i.e., inhibin A and inhibin B (18). A recent study showed that women with low day 3 serum inhibin-B concentrations demonstrate a poorer response to controlled ovarian hyperstimulation for IVF relative to women with high day 3 inhibin-B (19). Nevertheless, in that study women with low inhibin-B had mean basal FSH levels significantly higher than those found in women having high inhibin-B.

The above notwithstanding, normal baseline hormonal values never guarantee that an endocrine system is functioning normally. Indeed, patients with baseline values in the normal range may have a diminished ovarian reserve (6,7). Thus, a number of provocative tests have been devised to assess ovarian reserve indirectly and unmask patients who might not be detected by basal hormone screening alone. These include the clomiphene citrate challenge test and the gonadotropin releasing hormone (GnRH) agonist stimulation test (1). However, whether these indirect provocative tests are more informative of ovarian reserve than basal FSH remains unclear (20). On the other hand, neither basal hormonal measurements nor such dynamic tests provide direct information concerning the responsiveness of the ovaries to the exogenous gonadotropins used in ovarian stimulation for IVF. In fact, recent studies propose the clinical response to gonadotropin treatment as the more direct way to assess ovarian reserve and the better predictor of fertility potential (6,21). These studies, however, were retrospective analyses of IVF cycles.

The need for prospective studies and for the performance of other stimulation tests to be clearly compared with that of basal FSH concentration has been stressed (1,20). In this respect, there is only one previous report investigating prospectively the ovarian response to exogenous gonadotropin administration and comparing it to basal FSH in IVF patients. Franchin *et al.* (22) evaluated the E_2 response 24hr after exogenous FSH injection in 52 IVF patients. Two menstrual cycles later, ovarian stimulation was performed for IVF, using GnRH agonist and hMG. A good correlation between exogenous FSH ovarian reserve test (EFORT) and the subsequent quality of the ovarian response to stimula-

tion for IVF was observed. The concomitant analysis of two parameters (the size of the post-FSH plasma E_2 increment coupled with basal FSH concentrations) allowed identification of good IVF responders in 90% of cases. Similarly, EFORT could detect 81% of the poor IVF responders. The predictive value of basal FSH alone was significantly lower: 60 and 45% of good responders and poor responders, respectively (22).

In the work by Franchin *et al.* (22), however, criteria for the analysis of the EFORT results were based on a retrospective evaluation of a previous pilot study in 18 IVF candidates. Thus, three groups of patients were considered: normal, intermediate, and poor ovarian response groups. It is of note that the mean peak E_2 concentration during gonadotropin follicular stimulation in the intermediate ovarian response group was as much as 2000 pg/ml. Furthermore, only 11 women had their IVF cycles canceled. In addition, neither sensitivity nor specificity for the EFORT test was provided. On the other hand, it has been stressed that a 24-hr interval seems short to obtain a representative ovarian response (19). Finally, the work by Franchin *et al.* (22) has not been reproduced by others.

In the present prospective study women received 5 days of gonadotropin ovarian stimulation with hMG, and multivariate logistic regression and ROC analyses of the results were used to discriminate between canceled and punctured IVF cycles. Our results indicate that the predictive power of this dynamic test of ovarian reserve is better than that of basal hormone values (FSH and inhibin) and it is based mainly on the E_2 response to hMG treatment. However, given that the diagnostic accuracy of the hMG ovarian reserve test still fails in as many as 23% of patients, E_2 concentrations are poorly reproducible, thus precluding the definition of reference values for daily practice, and FSH determination is simple, inexpensive, not time-consuming, and easily repeatable, the superiority, if any, of the hMG or any dynamic test over basal hormone determinations in predicting IVF performance in the daily clinical setting remains to be established. This is further stressed by the fact that woman's age was a stronger predictor of pregnancy after IVF than the hMG test or basal hormonal levels in the present study. This is in agreement with some previous reports on the subject (23) but it is in contrast to others (3).

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REFERENCES

1. Scott RT, Hofmann GE: Prognostic assessment of ovarian reserve. *Fertil Steril* 1995;63:1–11
2. Scott RT, Toner JP, Muasher SJ, Oehninger S, Robinson S, Rosenwaks Z: Follicle-stimulating hormone levels on cycle day 3 are predictive of in vitro fertilization outcome. *Fertil Steril* 1989;51:651–654
3. Toner JP, Philput CB, Jones GS, Muasher SJ: Basal follicle stimulating hormone level is a better predictor of in vitro fertilization performance than age. *Fertil Steril* 1991;55:784–791
4. Cahill DJ, Prosser CJ, Wardle PG, Ford WCL, Hull MGR: Relative influence of serum follicle stimulating hormone, age and other factors on ovarian response to gonadotrophin stimulation. *Br J Obstet Gynaecol* 1994;101:999–1002
5. Balasch J, Creus M, Fábregues F, Carmona F, Casamitjana R, Ascaso C, Vanrell JA: Inhibin, follicle-stimulating hormone, and age as predictors of ovarian response in in vitro fertilization cycles stimulated with gonadotropin-releasing hormone agonist-gonadotropin treatment. *Am J Obstet Gynecol* 1996;175:1226–1230
6. Farhi J, Homburg R, Ferber A, Orvieto R, Ben Rafael Z: Non-response to ovarian stimulation in normogonadotrophic, normogonadal women: A clinical sign of impending onset of ovarian failure pre-empting the rise in basal follicle stimulating hormone levels. *Hum Reprod* 1997;12:241–243
7. Kim MR: Screening for ovarian reserve. *Assist Reprod Rev* 1998;8:17–22
8. McDonough PG, Mahesh VB, Byrd JR: The diagnostic use of gonadotropins. *Fertil Steril* 1970;21:126–133
9. Netter A, Millet D, Salomon-Bernard Y: Ovarian stimulation tests using human menopausal gonadotropin (HMG). *J Reprod Fertil* 1970;21:313–317
10. Hanley JA, McNeil BJ: The meaning and use of the area under receiving operating characteristic (ROC) curve. *Radiology* 1982;143:29–36
11. Zweig MH, Campbell G: Receiver-operating characteristic (ROC) plots: A fundamental evaluation tool in clinical medicine. *Clin Chem* 1993;39:561–577
12. Balasch J, Fábregues F, Creus M, Moreno V, Puerto B, Peñarubia J, Carmona F, Vanrell JA: Pure and highly purified follicle-stimulating hormone alone or in combination with human menopausal gonadotrophin for ovarian stimulation after pituitary suppression in in-vitro fertilization. *Hum Reprod* 1996;11:2400–2404
13. Fábregues F, Balasch J, Creus M, Cívico S, Carmona F, Puerto B, Vanrell JA: Long-term down-regulation does not improve pregnancy rates in an in vitro fertilization program. *Fertil Steril* 1998;70:46–51
14. Burger HG, Groome NP, Robertson DM: Both inhibin A and B respond to exogenous follicle-stimulating hormone in the follicular phase of the human menstrual cycle. *J Clin Endocrinol Metab* 1998;83:4167–4169
15. Balasch J, Jové IC, Moreno V, Cívico S, Puerto B, Vanrell JA: The comparison of two gonadotropin-releasing hormone agonists in an in vitro fertilization program. *Fertil Steril* 1992;58:991–994
16. de Mouzon J, Lancaster P, and the International Working Group for Registers on Assisted Reproduction: World collaborative report on in vitro fertilization. Preliminary data for 1995. *J Assist Reprod Genet* 1997;14:251S–265S
17. Schattman GL, Davis OK, Rosenwaks Z: Patient selection and screening for assisted reproductive technology. *Infertil Reprod Med Clin North Am* 1993;4:619–641
18. Groome NP, Illingworth PJ, O'Brien M, Pai R, Rodger FE, Mather J, McNeilly AS: Measurement of dimeric inhibin B throughout the menstrual cycle. *J Clin Endocrinol Metab* 1996;81:1401–1405
19. Seifer DB, Lambert-Messerlian G, Hogan JW, Gardiner AC, Blazar AS, Berk CA: Day 3 serum inhibin-B is predictive of assisted reproductive technologies outcome. *Fertil Steril* 1997;67:110–114
20. Galtier-Dereure F, De Bouard V, Picot MC, Vergnes C, Humeau C, Bringer J, Hedon B: Ovarian reserve test with the gonadotropin-releasing hormone agonist buserelin: Correlation with in-vitro fertilization outcome. *Hum Reprod* 1996;11:1393–1398
21. Roest J, van Heusden AM, Mous H, Zeilmaker GH, Verhoeff A: The ovarian response as a predictor for successful in vitro fertilization treatment after the age of 40 years. *Fertil Steril* 1996;66:969–973
22. Franchin R, de Ziegler D, Olivennes F, Taieb J, Dzik A, Frydman R: Exogenous follicle stimulating hormone ovarian reserve test (EFORT): A simple and reliable screening test for detecting “poor responders” in in-vitro fertilization. *Hum Reprod* 1994;9:1607–1611
23. Sharif K, Elgendy M, Lashen H, Afnan M: Age and basal follicle stimulating hormone as predictors of in vitro fertilisation outcome. *Br J Obstet Gynaecol* 1998;105:107–112