Comparisons of inhibin B versus antimüllerian hormone in poor ovarian responders undergoing in vitro fertilization

Rongrong Tan, M.M.Sc., Danhua Pu, M.M.Sc., Lipeng Liu, M.M.Sc., Jiayin Liu, M.D., Ph.D., and Jie Wu, M.D., Ph.D.

The State Key Laboratory of Reproductive Medicine, Department of Obstetrics and Gynecology, The First Affiliated Hospital of Nanjing Medical University, Nanjing Medical University, Nanjing, People's Republic of China

Objective: To evaluate serum inhibin B as a predictor of poor ovarian response in patients undergoing in vitro fertilization/intracytoplasmic sperm injection (IVF-ICSI) and to compare it with the performance of antimüllerian hormone (AMH).
Design: Meta-analysis.
Setting: University hospital.
Patient(s): Patients undergoing IVF.
Intervention(s): None.
Main Outcome Measure(s): Poor ovarian response in controlled ovarian hyperstimulation (COH).
Result(s): Fifteen studies on serum inhibin B and 12 studies on AMH were selected for meta-analysis. Both basal and stimulated inhibin B levels were statistically significantly lower in poor ovarian responders than in controls. The estimated summary receiver operating characteristic (ROC) curves suggested that stimulated inhibin B was more accurate than basal inhibin B and AMH in the prediction of poor ovarian response.
Conclusion(s): Both basal and stimulated serum inhibin B levels are lower in poor responders than in controls. Compared with AMH, stimulated inhibin B is a more accurate predictor of ovarian response in patients undergoing IVF, making it a potentially useful tool in future IVF practice. (Fertil Steril® 2011;96:905–11. ©2011 by American Society for Reproductive Medicine.)

Key Words: Antimullerian hormone, in vitro fertilization, inhibin B, poor ovarian response, meta-analysis

In vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) are widely accepted as effective treatments for most causes of infertility. Generally, for IVF to be successful, adequate follicular recruitment and maturation are essential. The first poor responder was described in 1983, when Garcia et al. (1) assessed a poor responder who had a low peak estradiol level (1). Most clinicians now regard poor ovarian response to be those patients with <500 pg/L peak estradiol levels and/or <4 dominant follicles on the day of human chorionic gonadotropin (hCG) administration, in whom a smaller number of embryos are thus transferred. It is estimated that the incidence of poor response varies from 9% to 24% (2). Poor ovarian response is defined as reduced follicle/oocyte production after controlled ovarian hyperstimulation (COH) in IVF treatment (2, 3). In comparison with normal responders, these patients have impaired fertilization rates and lower embryo quality (4). Moreover, the poor response to ovulation induction results in high cancellation and failure rates, which greatly influences overall IVF success rates as well as cost effectiveness (2). Therefore, the prediction of poor responders has been one of the most difficult challenges in assisted reproductive technology (ART) as these patients have disappointing overall IVF success rates.

Currently, the clinical markers used for evaluating ovarian response are the basal hormone test in the early follicular phase to measure concentrations of follicle-stimulating hormone (FSH), estradiol, and the FSH to luteinizing hormone (LH) ratio, dynamic tests, and basal ultrasonographic measurements such as the antral follicle count (5) and ovarian volume (6). Although the basal assays preferentially reflect the size of the ovarian follicle pool at rest, the glandular response to stimulation may provide a more useful assessment of the reserve of the endocrine organ in question than any basal hormone measurement (7). Thus, some investigators have proposed measuring the dynamic variations of serum inhibin B or antimüllerian hormone (AMH) under FSH treatment (8–11).

Both inhibin B and AMH are members of the transforming growth factor-β family, and they are produced in the granulosa cells of small antral follicles (12, 13). As such, they are thought to be more direct and precise assessors of the ovarian reserve (8, 10). Riggs et al. (14) demonstrated that AMH correlates better with the number of retrieved oocytes than with age, FSH, LH, and estradiol. Receiver operating characteristic (ROC) curves estimate that the AMH concentration accurately predicts ovarian responsiveness to COH with high sensitivity and specificity. Recently, a study reported that day-5 inhibin B was a better predictor of ovarian response than basal FSH and both basal and day-5 estradiol levels (15). However, the studies comparing the accuracy of serum inhibin B and AMH levels as a predictor of poor ovarian response have yielded conflicting results (10, 16, 17): the three respective studies demonstrated that AMH was better than, equal to, and worse than inhibin B as a marker of ovarian response to COH. Our meta-analysis assesses the true accuracy of inhibin B as a prognostic factor for ovarian response in IVF-ICSI treatment and explores whether inhibin B is superior to AMH.

Received June 14, 2011; revised July 13, 2011; accepted July 14, 2011; published online August 16, 2011.
R.T. has nothing to disclose. D.P. has nothing to disclose. L.L. has nothing to disclose. J.L. has nothing to disclose. J.W. has nothing to disclose.
Reprint requests: Jie Wu, M.D., Ph.D., State Key Laboratory of Reproductive Medicine, Nanjing Medical University, 210029, Nanjing, People's Republic of China (E-mail: jie.wuyale@gmail.com).

MATERIALS AND METHODS

Search Strategy, and Inclusion and Exclusion Criteria

We searched MEDLINE (1950–2010) and EMBASE (1974–2010) in a systematic, diligent manner for all studies on inhibin B as a predictor of ovarian response in patients undergoing IVF-ICSI. The following keywords were used in our literature search: "inhibin B" and "in vitro fertilization" or "in vitro fertilisation" or "assisted" or "intracytoplasmic" or "intracytoplasmatic."

The references of all computer-identified publications were searched for additional studies, and the MEDLINE option "related articles" was used to search for other potentially relevant articles. Review articles and the references of other relevant studies that we had identified were hand-searched to find additional eligible studies. No uniform criteria for the definition of poor ovarian response could be applied; thus, the definitions of poor ovarian response involved cycle cancelation, number of dominant follicles, oocytes at retrieval below a certain threshold, or combinations of these. Also, any cutoff or set of cutoffs for an abnormal test result was included in the review and analysis. Articles published in all languages were finally selected if they met the following criteria: 2 × 2 tables comparing inhibin B levels and the occurrence of poor ovarian response could be constructed with their data.

To compare inhibin B with AMH, we updated our recently published meta-analysis on the performance of AMH (18). We searched the MEDLINE and EMBASE databases using the same basic series of keywords used in the previous search plus "anti-mullerian hormone" or "mullerian-inhibiting factor." The period was extended until December 2008. If new studies were suitable for meta-analysis according to the previously described procedure, they were added to the already selected studies. If a study on both inhibin B and AMH was collected by any of the search strategies, this study was used for both review groups.

Quality Assessment

We systematically assessed the characteristics of each eligible study: [1] data collection (prospective vs. retrospective), [2] study design (cohort study vs. case-control study), [3] analysis of one or multiple cycles per couple, [4] stimulation regimen (gonadotropin-releasing hormone [GnRH] agonist or GnRH antagonist), [5] definition of poor ovarian response, and [6] the assay used for inhibin B and AMH measurement.

Data Extraction and Conversion

For all finally selected articles, we extracted the following information: first author's name, region/country where the study was conducted, year of publication, and diagnostic criteria. In addition, we collated the number of poor/normal ovarian responses, the mean inhibin B concentrations, and the standard deviation. In addition, for each study, sensitivity and specificity were calculated from 2 × 2 tables. All data were independently abstracted in duplicate by two researchers. If the researchers disagreed, a final result was reached by discussion.

Statistical Analysis

Summary statistics were estimated in Review Manager 4.2 software (RevMan 4.2; The Nordic Cochrane Center, Rigshospitalet). Continuous variables were expressed as the standardized mean difference (SMD) with 95% confidence intervals (CIs). We used the Meta-Disc software (http://www.hrc.es/investigacion/metadisc-en.htm) to evaluate the true accuracy of inhibin B as a prognostic factor for the outcome of IVF-ICSI treatment compared with AMH. Sensitivity, specificity, and 2 × 2 tables were calculated from each enrolled study. $P<.05$ was considered statistically significant.

A test of heterogeneity between the studies was conducted using Cochran's Q test and Higgins I-squared statistic. A random effect model (DerSimonian and Laird method) was used if heterogeneity was observed (Q-statistic: $P<.10$; $I^2>50\%$), but the fixed effect model was applied in the absence of between-study heterogeneity (Q-statistic: $P>.10$; $I^2<50\%$). Publication bias was evaluated using a funnel plot. For meta-analysis of the test accuracy data, if the sensitivity and specificity were homogeneity, a summary point estimate of the sensitivity-specificity points and the 95% CI was calculated. If the studies were reasonably homogeneous, the accuracy estimates from individual studies would lie along a line corresponding to the pooled accuracy estimate. Large deviations from this line would indicate possible heterogeneity.

A meta regression analysis was used to evaluate whether the characteristics of the study were associated with the discriminatory capacity. If one of the study characteristics was found to have a statistically significant impact on the performance of the test, further analysis was performed in subgroups of patients. If not, it was explored whether the differences in sensitivity

TABLE 1

Serum inhibin B levels in poor ovarian responders and controls.

	Poor response			Normal response			
Study	Number	Mean	SD	Number	Mean	SD	*P* value
Basal concentration							
Peñarrubia J (9)	20	36.2	8	60	49.8	6.9	<.05
Muttukrishna S (11)	17	70	12.79	52	126.9	8.8	<.001
McIlveen M (16)	13	50	58	71	129	87	.002
Creus M (23)	40	39.91	23.14	80	53.35	29.61	<.05
Bancsi LF (24)	36	70	47	84	118	46	<.001
Tharnprisarn W (25)	20	113.18	57.96	40	94.05	61.81	NS
Eldar-Geva T (26)	7	79.4	19.8	32	137.9	210.6	NS
Kwee J (27)	29	76	47.4	81	93.1	43	.08
Wu CH (28)	14	51.1	86.4	46	79.3	63	.02
Jayaprakasan K (29)	15	58.7	62.6	120	51.6	28.7	.45
Chen Y (30)	8	37	35	29	91	90	.016
Stimulated concentration							
Peñarrubia J (9)	20	90.3	68.5	60	451.2	123.9	<.001
Peñarrubia J (15)	26	115	76.7	72	359.8	202.5	<.001
Eldar-Geva T (26)	40	136.2	40.4	32	222.7	268.7	NS
Chen Y (30)	8	194	157	29	2254	4765	.033

Note: NS= not statistically significant; SD = standard deviation.

Tan. Inhibin B versus AMH in poor responders. Fertil Steril 2011.