

Relationship of early follicular phase sera follicle stimulating hormone and luteinizing hormone levels as measured by a radioimmunoassay and an enzyme-linked immunosorbent assay to number of oocytes retrieved

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Summary: A study was performed to see if the level of serum follicle stimulating hormone (FSH) or luteinizing hormone (LH) obtained in the early follicular phase could predict the number of oocytes retrieved following in vitro fertilization (IVF). For each patient the sera FSH and LH were measured by both an enzyme-linked immunosorbent assay (ELISA) and a radioimmunoassay (RIA) method. With the ELISA method when early follicular phase serum FSH was \leq to the group median (9.0 mIU/mL) 16.5 oocytes were retrieved vs 6.7 when FSH was greater than the median. Comparable values using the median of the RIA assay were 17.5 vs 8.1 oocytes. Similar analysis for serum LH failed to show any relationship between baseline LH and the number of oocytes retrieved. This study thus demonstrates that at least one non-isotopic method is equal to a specific RIA method in distinguishing good from average or poor responders.

Key words: Ovarian response; In vitro fertilization; Non-isotopic assay; Gonadotropin.

INTRODUCTION

The value of measuring early follicular phase serum follicle stimulating hormone

(FSH) levels for in vitro fertilization (IVF) programs has been clearly established to help predict the number of oocytes that are likely to be retrieved (¹⁻³). High FSH levels may alert the clinician to either cancel the cycle or to consider utilizing a different controlled ovarian hyperstimulation regimen. However, differences of opinion may and often do occur as to what constitutes a "high" level. An absolute cut-off point established in one facility under highly controlled conditions (specimens drawn at exactly the same time, all specimens assayed in one run, etc.) may not exhibit as high a predictive value when utilized in other facilities under less ideal conditions. A relative cut-

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off established within each facility might prove more useful under actual clinical conditions.

A prospective study was designed to determine if sera FSH levels above the median determined for early follicular phase are predictive of the number of oocytes available for retrieval. Two additional questions we attempted to answer were 1) would the predictive value be consistent across assay methodologies? and 2) would sera luteinizing hormone (LH) levels be equally useful?

The study presented herewith attempted to determine if early follicular phase sera LH and FSH (as measured by traditional double antibody radioimmunoassay (RIA) and the newer automated enzyme-linked immunosorbent assay [ELISA]) would correlate with the number of oocytes retrieved in patients undergoing identical IVF controlled ovarian hyperstimulation regimens.

MATERIALS AND METHODS

Forty-seven consecutive patients seeking IVF treatment at a large university hospital were enrolled in the study. The patients agreed to have their medical records released for research purposes as long as their confidentiality was assured in compliance with the guidelines of the Institutional Review Board. Follicle stimulating hormone and LH levels were measured on day three of the patients' cycles using an ELISA by Boehringer Mannheim Corporation (BMC) (Indianapolis, IN) and an RIA by Diagnostic Products Corporation (DPC) (Los Angeles, CA). The inter-assay coefficients of variation were FSH (BMC): 2.3%; FSH (DPC): 5.6%; LH (BMC): 4.7%; and LH (DPC): 8.3%. The intra-assay coefficients of variation were FSH (BMC): 2.1%; FSH (DPC): 6.5%; LH (BMC): 3.8%; and LH (DPC): 3.6%.

All patients were placed on a controlled ovarian hyperstimulation regimen employing luteal phase leuprolide acetate for a minimum of 10 days followed by leuprolide acetate and 300 IU of human menopausal gonadotropins daily. Patients were monitored by periodic ultrasound and serum estradiol measurements. When a minimum of two follicles greater than 20 mm in

mean diameter with concomitant estradiol levels of 200 to 300 pg/mL per follicle were attained, 10,000 IU of human chorionic gonadotropin were administered. Retrieval was performed 36 hours after human chorionic gonadotropin.

The mean number of oocytes per retrieval and the median sera FSH and LH levels as determined by both assay methods were calculated. Patients were grouped according to median analyte level; the mean number of oocytes per group above and below the median FSH and LH levels were calculated. Data were analyzed by t-test with p value of < 0.05 to determine statistical significance.

RESULTS

Retrievals were performed in 45 of 47 enrolled patients. The ages ranged from 27 to 50 years with a mean of 34.7 ± 5.1 . The mean number of oocytes per retrieval was 14.3 ± 12.7 .

The correlation coefficient between the two FSH assays was 0.885 ($p < .001$) (Fig. 1). The group mean FSH levels in mIU/mL using the ELISA assay were 8.8 compared to 10.8 using the RIA. The median FSH levels were 9.0 and 11.0 mIU/mL, respectively. The correlation between FSH and the number of oocytes

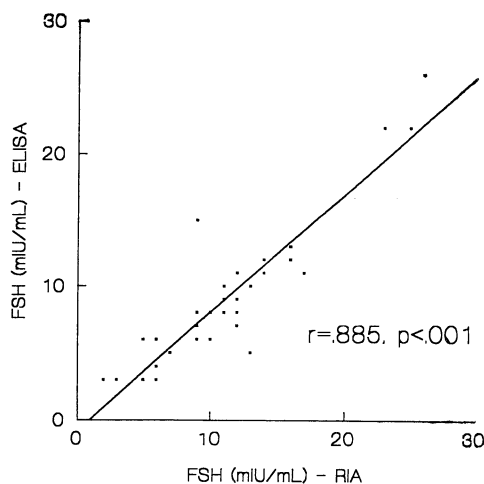


Fig. 1. — The correlation between an ELISA and a RIA assay of serum FSH.

retrieved, -0.468 ($p=.003$) using ELISA and -0.430 ($p=.008$) for RIA, indicates that the number of oocytes retrieved decreases as FSH increases (Fig. 2).

The mean number of oocytes per retrieval decreased to below ten at the median level of FSH regardless of the method used. Therefore, the patients were divided into two groups, group 1 having FSH levels equal to or less than the median and group 2 having FSH levels greater than the median. The ELISA group 1 patients had a mean of 16.5 oocytes retrieved vs 6.7 for group 2. The RIA group 1 had 17.5 oocytes retrieved vs 8.1 for group 2. Regardless of the assay used, there was a statistically significant ($p=.002$ and $p=.003$, respectively) increase in the mean number of oocytes retrieved when the patient's follicular FSH was at or lower than the group median.

Similar analysis for baseline LH levels failed to show any relationship between early follicular phase serum LH and the number of oocytes retrieved. The correlation coefficient between LH and number

of oocytes retrieved was 0.097 ($p=NS$) for the ELISA assay and 0.295 ($p=NS$) for RIA. Grouping patients by the median LH levels (ELISA: 4 mIU/mL, RIA: 7 mIU/mL), the mean number of oocytes retrieved was 13.7 for ELISA group 1 and 14.4 for group 2; for RIA, the mean number of oocytes were 12.4 and 15.5 for groups 1 and 2, respectively. In neither case were the differences statistically significant ($p>0.05$).

DISCUSSION

This study indicates that by determining the median serum FSH level prior to initiating controlled ovarian hyperstimulation in the early follicular phase for their patient population, IVF facilities can easily establish a cut-off value predictive of those patients who will produce the most oocytes for IVF. Sera LH levels do not seem useful.

Furthermore, the BMC non-isotopic assay and the DPC RIA were equally useful in distinguishing good from poor responders. The main disadvantage of using RIA assays, i.e., the need for radioactive waste disposal, can therefore be overcome. However, it is imperative that laboratories involved in the analysis of IVF patient specimens, when switching to non-RIA FSH assays, ensure that the new assay does not merely correlate across the assay range (including the high menopausal ranges), but that it is also accurate at the lower levels that are useful in predicting the number of follicles available in that cycle's cohort.

The mean age for the IVF patients at the Cooper Center for IVF was 34.7 . Possibly in IVF facilities using a younger population the median will not prove to be as adequate a method to determine the discriminating cut-off; certainly if they are using the BMC non-isotopic assay or the DPC RIA the levels that have been

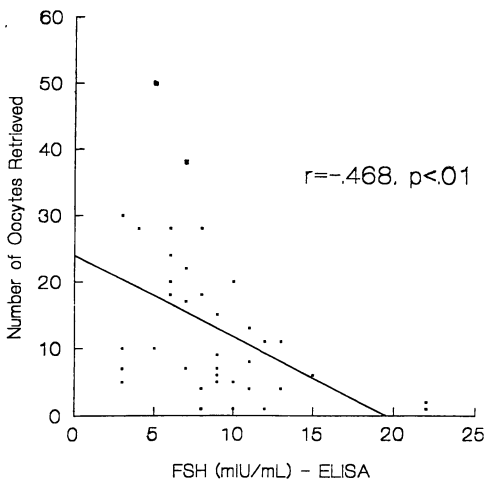


Fig. 2. — The correlation between early follicular phase FSH levels and the number of oocytes retrieved.

established in this manuscript would still be applicable to their age population. However, for other assays they may have to separately determine what FSH level distinguishes good from average or poor responders.

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