Preretrieval Predictors of Pregnancy in IVF

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Purpose: This study was designed to evaluate the predictive value of preretrieval parameters of ovarian stimulation in patients undergoing IVF-ET.

Methods: Women diagnosed with infertility due to tubal factor were compared to women with other and/or multiple diagnoses. Stepwise logistic regression evaluated 389 cycles to identify the best predictors of pregnancy among the following variables: age, primary or secondary infertility, cycle number, type and dose of gonadotropin, duration of gonadotropin administration, serum estradiol level, and number and size of follicles.

Results: In the tubal disease group, probability of pregnancy was greater in cycles with serum estradiol levels below 1100 pg/ml on the day of hCG (odds ratio, 4.7) and with administration of gonadotropins for less than 10 days (odds ratio, 3.7). In contrast, in the other/mixed diagnoses group, a serum estradiol below 1100 pg/ml was associated with a decreased probability of pregnancy (odds ratio, 0.6).

Conclusions: Optimal parameters of ovarian stimulation may vary according to the etiology of infertility. In patients with tubal disease, the beneficial effects of greater stimulation, and thus the greater number of available oocytes, may be offset by adverse effects on the endometrium and on the quality of oocytes and embryos. In contrast, in other diagnostic groups, the advantage of an increased number of oocytes may outweigh the potential adverse effects of prolonged stimulation and higher estradiol levels.

KEY WORDS: in vitro fertilization; controlled ovarian hyperstimulation; estradiol; gonadotropins.

INTRODUCTION

Controlled ovarian hyperstimulation (COH) is widely employed in in vitro fertilization-embryo transfer (IVF-ET) programs. Stimulation of release of endogenous gonadotropins by clomiphene citrate or the administration of exogenous gonadotropins promotes recruitment and maturation of a cohort of antral follicles (1). Thus, COH increases the probability of obtaining several oocytes and several embryos, resulting in improved pregnancy rates (2–5). Over the last several years, many IVF-ET programs have performed COH by administration of gonadotropins in conjunction with “long” protocols of GnRH agonists for hypothalamic-pituitary suppression. Hypothalamic-pituitary suppression with GnRH agonists has well-recognized benefits such as a reduced incidence of inadequate responses, protection from a premature LH surge, and a greater number of oocytes per retrieval (6–8).

The primary goal of COH in IVF-ET is to maximize the number of mature oocytes obtained. The duration of administration of gonadotropins and the timing of the administration of hCG are based on ultrasonographic criteria of follicular growth and on serum levels of estradiol. The typical minimum requirement for administration of hCG is the presence of at least two follicles measuring at least 16 mm with serum estradiol concentrations of at least 500 pg/ml (conversion factor to SI units, 3.671) (1). Many IVF-ET programs conduct aggressive COH in order to obtain the maximum number of oocytes. The rationale for this approach is provided by observations of a positive correlation between pregnancy rates, level of estradiol on the day of administration of hCG, number of follicles, size of leading follicles, and number of retrieved oocytes (4,5,9,10). These findings, however, contrast with other reports suggesting that fertilization rates, implantation rates, and pregnancy rates decline in cycles associated with a high number of preovulatory follicles and a high number of oocytes (11–13).

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These discrepancies in the relationship between pregnancy rates and parameters of COH are likely due to differences in the populations evaluated by individual studies and different protocols of COH. Factors such as underlying cause of infertility, age, and medications used during COH may play a significant role in altering patients' ovarian response, oocyte maturation, endometrial receptivity, and ultimately, chances of pregnancy.

Importantly, while many studies identified the underlying cause of infertility as a predictor of IVF-ET success, we are not aware of studies comparing potential predictors of pregnancy in individual diagnostic groups. In particular, it is not known whether the parameters of COH found to be optimal for patients with one cause of infertility remain optimal for patients with other causes of infertility.

This study was designed to evaluate the relationship between ovarian response to COH and pregnancy rates in patients with a single cause of infertility, tubal disease, compared to patients with other and/or mixed causes of infertility. We postulated that the optimal parameters of COH for patients with tubal disease may be different from those for other patients.

MATERIALS AND METHODS

Patient Population

We studied IVF cycles performed at Yale–New Haven Hospital between January 1990 and March 1994. The study evaluated only cycles using a long (suppression) GnRH analogue protocol (leuprolide acetate; Lupron; TAP Pharmaceuticals, Chicago, IL). Controlled ovarian hyperstimulation was carried out using either human menopausal gonadotropin (hMG; Pergonal, Serono Laboratories, Randolph, MA) alone or follicle-stimulating hormone (FSH; Metrodin, Serono Laboratories, Randolph, MA) alone. Cycles using clomiphene citrate, "short" GnRH analogue (flare-up) protocols, natural cycles, and cycles using a combination of hMG and FSH were excluded. Egg-donor and sperm-donor cycles were also excluded.

Patients were assigned to two groups on the basis of the etiology of their infertility: a tubal disease group and an other/mixed diagnostic group. Patients were assigned to the tubal disease group when laparoscopy and/or hysterosalpingography revealed tubal obstruction or peritubal/peri ovarian adhesions and no evidence suggesting other etiologies of infertility was present. The other/mixed diagnostic group consisted of patients

with evidence of ovulatory dysfunction, endometriosis, luteal-phase defect, and male-factor infertility and patients with unexplained infertility.

Clinical Variables

The study evaluated the following variables from each cycle of IVF: age of the female, type of infertility (primary or secondary), year of the IVF procedure, IVF cycle number, type of gonadotropin preparation used (Pergonal versus Metrodin), duration of gonadotropin administration, total amount of gonadotropin used per cycle, serum estradiol level on the day of hCG administration, number of follicles measuring at least 12 mm in average diameter on the day of hCG administration, and number of follicles measuring at least 16 mm in average diameter on the day of hCG administration. The primary outcome was chemical pregnancy defined as β -hCG above 10 mIU/ml when measured at least 14 days after administration of hCG. In addition, secondary outcomes were studied and included clinical pregnancy (defined by ultrasonographic documentation of fetal cardiac activity) and live birth.

Statistical Analysis

Univariate analysis consisted of evaluation of contingency tables with the aid of the likelihood-ratio chi-square test.

Stepwise logistic regression was used to determine which predictors best correlated with pregnancy (14). Potentially relevant variables were initially evaluated by univariate analysis using the likelihood-ratio test. Continuous variables were dichotomized when their relationship with outcome (probability of pregnancy) was better approximated by a binary rather than a linear function. The selection of threshold values for dichotomization was carried out using a modified receiver operating characteristic (ROC) curve analysis (15). In this method, the sum of the true positive rate and true negative rate is plotted as a function of different threshold values of a continuous variable. The cutoff points for dichotomization correspond to the peaks of such plots.

A variable was entered into the logistic regression model (forward step) when the comparison of the models (without and with the tested variable) resulted in a P value ≤ 0.10 ("alpha" level). A variable was excluded from the model (backward steps) when the comparison of the models (without and with the tested variable) resulted in a P value > 0.15 . Before the final

model was constructed, interactions between variables were evaluated. Interaction components were excluded from the final model when the comparison of the models (without and with the tested interaction component) resulted in a P value ≤ 0.15 . Important and widely recognized factors predicting IVF success (age of the female and number of embryos) were incorporated ("forced") into the final models to account for their possible interactions with other variables. Such a procedure aids in creating meaningful logistic regression models (14,16).

RESULTS

The study evaluated 105 cycles in the tubal disease group (67 patients) and 284 cycles in the other/mixed group (165 patients). The other/mixed group consisted of 42 cycles with evidence of male factor only, 7 cycles in patients with endometriosis only, 30 cycles in patients with anovulation only, and 32 cycles in patients with unexplained infertility; the remaining 173 cycles were performed in patients with more than one of the above diagnoses. The overall pregnancy rate per retrieval was 23.1%. The pregnancy rates in the tubal group and in the other/mixed group were, respectively, 28.6% (30 pregnancies in 105 cycles) and 21.1% (60 pregnancies in 284 cycles).

Univariate analysis demonstrated that in patients with tubal disease, serum estradiol level on the day of

administration of hCG and duration of administration of gonadotropins correlated with pregnancy. The relationship of both these variables with the pregnancy rate was not linear and was better approximated by binary functions. The dichotomization was carried out with the aid of ROC curve analysis and revealed the optimal cutoff points as follows: 1100 pg/ml for estradiol level and 9 days for duration of administration of gonadotropins.

Higher pregnancy rates in cycles with lower estradiol levels and a shorter course of gonadotropins could not be accounted for by differences in patient age, number of oocytes, fertilization rates, quality of transferred embryos, or number of transferred embryos (Table I).

In the tubal disease group, logistic regression modeling of pregnancy as a function of preretrieval parameters revealed that two variables were independently predictive of outcome: level of estradiol on the day of administration of hCG and duration of administration of gonadotropins. Other evaluated variables were non-contributory: age of the female, type of infertility (primary or secondary), year of the procedure, IVF cycle number, type of gonadotropin, total amount of gonadotropin used per cycle, number of follicles measuring at least 12 mm in average diameter on the day of hCG administration, and number of follicles measuring at least 16 mm in average diameter on the day of hCG administration. Since age is widely recognized as an important predictor of success of IVF, it was included

Table I. Selected Parameters of IVF in the Tubal-Factor Group and Other/Mixed Group Following Stratification According to the Level of Estradiol on the Day of Administration of hCG and Duration of Administration of Gonadotropins^{a,b}

Variable	Tubal group				Other/mixed group			
	A (N = 18)	B (N = 21)	C (N = 41)	D (N = 25)	A (N = 79)	B (N = 43)	C (N = 99)	D (N = 63)
Age	34.7 $\pm$ 0.8	35.3 $\pm$ 0.8	31.9 $\pm$ 0.6	36.4 $\pm$ 0.9	34.8 $\pm$ 0.5	36 $\pm$ 0.6	34.4 $\pm$ 0.4	35.7 $\pm$ 0.4
Number of follicles $\geq$ 12 mm in diameter	7.1 $\pm$ 0.8	6.0 $\pm$ 0.4	10.9 $\pm$ 0.4	8.2 $\pm$ 0.6	6.7 $\pm$ 0.3	5.5 $\pm$ 0.4	10.1 $\pm$ 0.3	9.0 $\pm$ 0.4
Number of follicles $\geq$ 16 mm in diameter	3.1 $\pm$ 0.4	3.3 $\pm$ 0.3	4.2 $\pm$ 0.5	3.2 $\pm$ 0.3	2.6 $\pm$ 0.2	3.1 $\pm$ 0.2	3.6 $\pm$ 0.2	4.5 $\pm$ 0.4
Number of oocytes	9.3 $\pm$ 1.3	4.3 $\pm$ 0.5	14.9 $\pm$ 1.0	8.7 $\pm$ 1.0	6.5 $\pm$ 0.4	4.9 $\pm$ 0.6	13.5 $\pm$ 0.7	9.6 $\pm$ 0.7
Percentage fertilization	79.9 $\pm$ 4.8	80.7 $\pm$ 6.0	72.2 $\pm$ 3.8	77.0 $\pm$ 4.6	64.6 $\pm$ 3.5	74.3 $\pm$ 5.4	58.9 $\pm$ 3.2	63.9 $\pm$ 3.7
Number of postmature oocytes	2.1 $\pm$ 0.7	0.8 $\pm$ 0.3	3.0 $\pm$ 0.3	0.7 $\pm$ 0.2	2.0 $\pm$ 0.2	0.7 $\pm$ 0.2	2.8 $\pm$ 0.4	1.0 $\pm$ 0.3
Number of transferred embryos	4.1 $\pm$ 0.2	3.0 $\pm$ 0.3	4.4 $\pm$ 0.3	4.1 $\pm$ 0.3	3.1 $\pm$ 0.2	3.1 $\pm$ 0.3	3.6 $\pm$ 0.2	3.9 $\pm$ 0.2
Average grade of transferred embryos	2.0 $\pm$ 0.2	1.7 $\pm$ 0.2	2.0 $\pm$ 0.1	2.0 $\pm$ 0.1	1.9 $\pm$ 0.1	2.1 $\pm$ 0.1	1.8 $\pm$ 0.1	2.1 $\pm$ 0.1

^a Each diagnostic group was stratified as follows: A, cycles with an estradiol level below 1100 pg/ml and administration of gonadotropins for less than 10 days; B, cycles with an estradiol level below 1100 pg/ml and administration of gonadotropins for 10 days or more; C, cycles with an estradiol level equal or greater than 1100 pg/ml and administration of gonadotropins for less than 10 days; D, cycles with an estradiol level equal or greater than 1100 pg/ml and administration of gonadotropins for 10 days or more.

^b Results are presented as mean $\pm$ SE.

Table II. Logistic Regression Models for Patients with Tubal Disease (Preretrieval Parameters Only)

Predictor	Outcome: odds ratio (95% confidence interval)		
	Chemical pregnancy	Clinical pregnancy	Live birth
Estradiol <1100 pg/ml	4.7 (1.7–12.9)	8.5 (2.4–30)	7.9 (2.1–30.0)
Induction for <10 days	3.7 (1.3–10.7)	3.6 (1.1–12.3)	6.1 (1.5–26)
Age	1 (0.9–1.1)	1.1 (0.9–1.3)	1 (0.8–1.1)

in the final models presented in Table II. Even when the age is accounted for, estradiol level on the day of administration of hCG and duration of administration of gonadotropins remained as significant independent predictors of chemical pregnancy, clinical pregnancy, and live birth. The probability of all these outcomes was significantly increased in cycles with estradiol levels below 1100 pg/ml and with durations of administration of gonadotropins of less than 10 days.

Comparable logistic regression modeling of pregnancy was carried out in cycles with other/mixed diagnoses. Level of estradiol on the day of administration of hCG was the only variable predictive of chances of pregnancy. The final model (with a correction for age) is presented in Table III. This model predicts that pregnancy rates in this group of patients is lower in cycles with estradiol levels below 1100 pg/ml. Furthermore, logistic regression analysis was performed in the subpopulation of the above patients by excluding the couples with male factor and polycystic ovary syndrome. This group of patients also had decreased chances of pregnancy (odds ratio, 0.43; 95% confidence interval, 0.18–1.01) when estradiol was below 1100 pg/ml.

Table III. Logistic Regression Models for Patients with Mixed/Other Diagnoses (Preretrieval Parameters Only)

Predictor	Outcome: odds ratio (95% confidence interval)		
	Chemical pregnancy	Clinical pregnancy	Live birth
Estradiol <1100 pg/ml	0.6 (0.3–1.1)	0.5 (0.2–1.1)	0.5 (0.2–1.1)
Induction for <10 days	1.1 (0.6–1.9)	1.3 (0.7–2.7)	1.6 (0.7–3.5)
Age	1 (0.9–1.1)	1 (0.9–1.1)	1 (0.9–1.1)

Figure 1 shows 95% confidence intervals of odds ratio for pregnancy in cycles with estradiol levels below 1100 pg/ml versus cycles with estradiol levels greater than or equal to 1100 pg/ml. Comparison of these 95% confidence intervals for tubal group and other/mixed group reveals that these intervals do not overlap. Consequently, these diagnostic groups have different distributions of probability of pregnancy as a function of estradiol level at the time of administration of hCG.

Since the number of transferred embryos may significantly affect pregnancy rates, logistic regression analysis was also repeated for both diagnostic groups, accounting for the number of transferred embryos. In the group of patients with tubal disease, the number of transferred embryos had no independent predictive power, while an estradiol level below 1100 pg/ml and a duration of gonadotropin administration of less than 10 days were predictive of higher pregnancy rates (Table IV). In patients with mixed/other diagnoses of infertility, a greater number of embryos improved pregnancy rates (Table V).

DISCUSSION

This study has demonstrated that in patients undergoing IVF-ET, predictors of success depend upon the

Fig. 1. Comparison of effects of estradiol level (on the day of administration of hCG) on the probability of chemical pregnancy in patients with tubal disease and patients with other or mixed diagnoses. Odds ratios of pregnancy rates were estimated for low vs high estradiol levels. Serum estradiol was considered low at levels below 1100 pg/ml and high at levels equal to or above 1100 pg/ml.

Table IV. Logistic Regression Models for Patients with Tubal Disease (Accounting for Number of Transferred Embryos)

Predictor	Outcome: odds ratio (95% confidence interval)		
	Chemical pregnancy	Clinical pregnancy	Live birth
Estradiol <1100 pg/ml	4.5 (1.6–12.6)	8.5 (2.4–30)	7.9 (2.1–30.0)
Induction for <10 days	3.9 (1.3–11.7)	3.5 (1–12.8)	6.1 (1.4–27.4)
Age	1 (0.9–1.1)	0.9 (0.8–1.1)	1 (0.8–1.1)
Number of embryos transferred	0.9 (0.7–1.3)	1 (0.7–1.5)	1 (0.7–1.5)

underlying etiology of infertility. In particular, we have observed that (i) patients with tubal disease have increased chances of pregnancy in cycles with a lower serum estradiol level and a shorter duration of administration of gonadotropin and (ii) patients with other/mixed diagnoses have increased chances of pregnancy in cycles with a higher serum estradiol level.

The present study traced pregnancies from implantation to delivery by analysis of three outcomes: chemical pregnancy, clinical pregnancy, and ultimately live birth. For all these outcomes the conclusions remained essentially unchanged, suggesting that for a given diagnostic group, increased probability of implantation ultimately leads to increased probability of live birth.

The present findings raise the interesting possibility that individualization of COH protocols according to the etiology of infertility may improve pregnancy rates. Patients with tubal disease may benefit from shorter exposure to gonadotropins and administration of hCG in the presence of lower levels of estradiol, while patients with other disorders of reproductive function

may have a greater chance of pregnancy following COH, leading to higher levels of estradiol. The present study provides some support for this hypothesis. The highest pregnancy rates in the tubal disease group were achieved in patients with estradiol levels below 1100 pg/ml and gonadotropins administered for less than 10 days; this group was characterized by cycles with relatively few follicles (at the time of hCG administration) and relatively few oocytes retrieved (Table I, group A vs others). Furthermore, the results of logistic regression held after accounting for the number of transferred embryos: estradiol level and duration of gonadotropin administration retained their predictive power (Table IV). Consequently, it appears that administration of hCG earlier in COH (in spite of fewer mature follicles) may result in a greater chance of success. Of course, the ultimate validation of this hypothesis would require that individual diagnostic populations be evaluated in a prospective, randomized study using different COH protocols.

Alternatively, our findings in patients with tubal disease may be explained by postulating intrinsic differences in ovarian response to COH by different patients (or by the same patients in different cycles). Thus, the chances of pregnancy may be higher when ovaries respond to COH earlier and when maturation of a sufficient number of preovulatory follicles occurs with concomitant development of only a few intermediate follicles and thus relatively low levels of estradiol. Conversely, unsuccessful cycles may be characterized by delayed maturation of dominant follicles with simultaneous development of a greater number of intermediate follicles and, consequently, higher levels of estradiol. In order to achieve a sufficient number of preovulatory follicles to fulfill the standard criteria for hCG administration, some ovaries may require longer stimulation than others. Since large follicles would be expected to provide higher-quality oocytes than intermediate follicles, COH cycles with fewer intermediate follicles would produce a greater proportion of high-quality oocytes than cycles with a large number of intermediate follicles. In addition, high estradiol levels (produced by large numbers of follicles) may have an adverse effect on the quality of oocytes, embryos, and endometrium (12,17).

Sharma *et al.* observed that in IVF-ET cycles resulting in retrieval of 10 or more oocytes, the implantation rate declined irrespective of fertilization rate (12). The authors of this study suggested that, in excessively stimulated cycles, the quality of oocytes and embryos or uterine responsiveness may be suboptimal. Other studies have demonstrated that an

Table V. Logistic Regression Models for Patients with Mixed/Other Diagnoses (Accounting for Number of Transferred Embryos)

Predictor	Outcome: odds ratio (95% confidence interval)		
	Chemical pregnancy	Clinical pregnancy	Live birth
Estradiol <1100 pg/ml	0.7 (0.4–1.2)	0.6 (0.3–1.3)	0.6 (0.3–1.3)
Induction for <10 days	1.1 (0.6–2)	1.4 (0.7–3.1)	1.8 (0.8–8.4)
Age	1 (0.9–1.1)	1 (0.9–1.1)	1 (0.9–1.1)
Number of embryos transferred	1.2 (1–1.4)	1.3 (1.1–1.6)	1.4 (1.1–1.7)

increase in estradiol level during COH is associated with out-of-phase (advanced) endometrial maturation and a reduction in the concentrations of estrogen and progesterone receptors (18,19). The adverse effect of excessive ovarian stimulation on oocyte quality has been suggested by the observation that an increased number of preovulatory follicles was associated with a lower proportion of cleaved oocytes and lower pregnancy rates (13).

In the present study patients with tubal disease were compared and contrasted with patients having other and mixed diagnoses. Patients with tubal disease were selected since they constituted the largest group with a single etiology of infertility; furthermore, these patients have presumably normal ovarian and endometrial function, and their male partners have normal parameters of semen analysis. IVF-ET in these patients is thought to be an ideal tool for bypassing the diseased organ (tubes) while utilizing other, healthy, components of the reproductive system: ovaries, endometrium, and sperm. COH in these patients may adversely affect ovarian (oocytes) and endometrial function.

In contrast to the tubal disease group, most other patients undergoing IVF-ET suffer from disorders affecting the ovaries, endometrium, and/or sperm. These patients generally have lower success rates than those with tubal disease. Since the abnormally functioning components of the reproductive system are not bypassed by IVF-ET, these patients may benefit from an increase in number of follicles and oocytes (Table I), which may increase the chance of obtaining a sufficient number of good-quality embryos and thus may improve the chance of pregnancy.

The observation of a decreased probability of pregnancy in cycles with lower levels of estradiol in patients with "other and mixed" diagnoses may be disproportionately affected by the inclusion of two unique populations of patients: women with PCO and men with male factor. Women with PCO typically have an exaggerated response to COH, with high estradiol levels and a large number of developing follicles. Thus, the inclusion of these patients significantly affects the distribution of these parameters in the studied population. Couples with male factor typically have a significantly lower fertilization rate and may therefore particularly benefit from an increased number of retrieved oocytes. Consequently, a separate analysis was carried out on patients with "other and mixed" diagnoses, excluding couples with PCO and male factor. Interestingly, the exclusion of these couples did not significantly affect the results of the analysis, and cycles with lower levels of estradiol still had a decreased probability of pregnancy.

The retrospective nature of this study warrants caution in extrapolation of the findings. Nevertheless, the use of logistic regression modeling offers significant protection from various sources of bias. Thus, several potential confounders, such as primary or secondary infertility, IVF cycle number, and ovarian stimulation with different gonadotropins, were evaluated and, in this study, had no significant effect on the outcome.

In conclusion, this study has provided evidence suggesting that preretrieval parameters of COH may differentially predict the outcome of IVF-ET in individual diagnostic categories. Further prospective studies should be designed to determine whether COH should be individualized according to the underlying etiology of infertility.

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