Multivariate Analysis of Factors Predictive of Successful Live Births in In Vitro Fertilization (IVF) Suggests Strategies to Improve IVF Outcome¹

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Purpose: Our purpose was (1) to identify characteristics correlated with pregnancy outcome, (2) to use these characteristics to predict in vitro fertilization (IVF) outcome, and (3) to develop strategies that might improve IVF success.

Methods: Maternal age, cause for IVF, donor insemination, rank of attempt, serum estradiol and luteinizing hormone levels on the day of human chorionic gonadotropin administration, flexible vs rigid catheter, number of embryos transferred of each morphologic type, and cell number were analyzed by logistic regression.

Results: Variables positively correlated with success are as follows: (1) for pregnancy, endometriosis and 2-, 3-, and 4-cell good and 4-cell excellent embryos; (2) for live births, 2-, 3-, and 4-cell good and 4-cell excellent embryos and donor insemination; and (3) for multiple births, 2- and 4-cell good and 4-cell excellent embryos. Maternal age was negatively correlated with live births.

Conclusions: Embryos derived from IVF have different potentials for implantation, live births, and multiple births. Transferring one additional good-quality embryo for each 5 years of incremental increase in maternal age is predicated to improve live birth rates without increasing multiple births.

KEY WORDS: in vitro fertilization; in vitro fertilization prediction; embryo quality; embryo cell number; endometriosis; multivariate analysis.

INTRODUCTION

A number of factors have been suggested to influence pregnancy rates in in vitro fertilization (IVF) either

positively or negatively (1–7). A relative quantitation of the strength of each factor in increasing or decreasing pregnancy rates would provide the basis for the development of a flexible individualized IVF approach and improve patient counseling. This potentially can offer the best chance of success in each cycle to each couple. Within this context we evaluated several parameters that may be associated with IVF success including the woman's age, cause for intervention, use of donor sperm, and characteristics of the given cycle such as rank of attempt, cycle hormonal profile, and use of rigid versus flexible catheter, as well as the results of gamete fusion represented by the number, quality, and developmental stage of embryos transferred. To minimize the potential effects of different ovarian stimulation protocols on the characteristics of endometrial receptivity, all study patients underwent ovarian hypostimulation by the same protocol (8). The end points considered were the pregnancy rates, live birth rates, and multiple birth rates. The anticipated interrelation among the examined factors imposes the use of multivariate analysis to eliminate the influence of confounding factors.

The objectives of this study were therefore (a) to identify patient, cycle, and embryo characteristics which are correlated with pregnancy outcome using multivariate analysis; (b) to use these characteristics to predict IVF outcome, and (c) to develop strategies that might improve IVF success for a given patient. Identifying variables that are significantly linked with IVF success would be of help in predicting the pregnancy outcome and therefore modifying, if possible, the IVF strategy in a way to maximize the odds for success. Moreover, in evaluating variables that can contribute to multiple births, our goal was to explore for each patient tactics aimed at increasing the chances for a live birth without a further increase in multiple births.

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MATERIALS AND METHODS

The study included 544 consecutive cycles, initiated at Boston IVF, that resulted in at least one embryo transfer. All patients underwent ovarian hyperstimulation by the same protocol: human menopausal gonadotropins (Pergonal and/or Metrodin; Serono, Braintree, MA) starting on cycle day 2 in conjunction with the gonadotropin releasing hormone (GnRH) analogue leuprolide acetate starting on cycle day 1 at a dose of 250 or 500 mg sc daily. Cycle monitoring was conducted by vaginal ultrasound and serum luteinizing hormone (LH) and estradiol (E_2). When three follicles approached a mean diameter of 18 mm, 10,000 IU human chorionic gonadotropin (hCG; Profasi; Serono) was given and transvaginal oocyte retrieval was performed 34–36 hr later. Sperm was processed by standard Percoll. Oocytes were inseminated with 1.5×10^5 or 5×10^5 motile sperm in droplets under mineral oil. Embryo transfer was performed 48 hr after oocyte retrieval. All embryos were evaluated with an inverted microscope (magnification, $\times 20$). The number and quality of blastomeres were assessed immediately prior to transfer. Embryo quality was graded according to the size, appearance, refractility, and fragmentation of the blastomeres and categorized into three groups. Embryos with evenly sized blastomeres of a nearly spherical appearance with moderate refractility and less than 10% fragmentation were graded as excellent. Those with more uneven or irregular-shaped blastomeres with mild variation in refractility and no more than 10% fragmentation were graded as good. Embryos with more than 10% fragmentation and uneven blastomeres and that were grossly variant in refractility were graded as poor.

All patients received luteal-phase support with progesterone (50 mg daily im or 100 mg in vaginal suppositories bid) from the day after embryo transfer. Progesterone supplementation was continued in the case of pregnancy until the tenth week of gestation only in women with luteal-phase deficiency, proven by endometrial biopsy. Clinical pregnancies included those that showed fetal heart movements, ectopics, and cases with normally rising levels of serum hCG in three consecutive measurements.

Statistical analysis involved univariate comparisons between the unsuccessful cycles and those that led to clinical pregnancies, those that resulted in live births, and those that involved multiple birth delivery using Student's *t* test and χ^2 . Since pregnancy outcome is influenced by multiple factors, most of which are inter-related, a second set of analysis was performed using

logistic regression entering all variables unconditionally into a maximum-likelihood fitting model. The dependent variables were dichotomous: pregnancies, live births, and multiple birth deliveries versus IVF failure. Independent variables included maternal age, cause for intervention, donor insemination, rank of attempt, serum LH and E_2 levels on the day of hCG administration, embryo transfer catheter (flexible vs rigid type), and number of embryo transferred of each morphologic type and developmental stage. Using the variables that were significantly correlated with pregnancy outcome, we attempted to predict the probabilities that patients have of achieving pregnancies, live births, and multiple births in a given cycle. The probability of each pregnancy end point (*p*) is given by the equation: $p = 1 / (1 + e^{(-P)})$, where $e^{(-P)}$ indicates that the base of the natural logarithm (2.718) is taken to the power of *P*, in which *P* is a linear formula derived from the regression coefficients of the significant variables (9).

RESULTS

Univariate Analysis

Table I provides a description of each patient, each cycle, and transferred embryo characteristics among the groups of women who become pregnant, had live births, and had multiple births analyzed on an IVF cycle outcome basis. Univariate analysis of each characteristic between these groups and the group with unsuccessful IVF cycles revealed some significant differences. The mean age of women who achieved pregnancy and delivered babies was significantly lower than that of women with failure. Of the variables describing the cause for IVF, male factor was less frequent in the pregnant group, although this difference was not significant for the group with live and multiple births. Endometriosis without tubal occlusion was more frequent among women with pregnancy and live births. All other causes for intervention were unrelated to pregnancy outcome (Table I).

Regarding the features of the stimulation cycle, multiple births were more frequent in the first IVF cycle. Serum levels of LH and E_2 on the day of hCG administration had no correlation with IVF outcome. Cycles that resulted in pregnancy as well as in live and multiple births were characterized by a higher mean number of embryo transferred. Analyzing the embryos transferred according to quality and number of blastomeres we found that only good-quality embryos at the 2-,

Table I. Patient, Cycle, and Embryo Characteristics According to IVF Cycle Outcome

	Failure	Pregnancy	<i>P</i> value	Live births	<i>P</i> value	Multiple births	<i>P</i> value
No. of cycles (total, 544)	380 (69.8) ^a	164 (30.2)		76 (14.0)		29 (5.3)	
Age	35.5 ± 0.2 ^b	34.3 ± 0.3	0.001	33.8 ± 0.4	0	33.2 ± 0.7	0.002
Tubal factor	225 (59.1)	88 (54.0)	NS ^c	37 (48.7)	NS	14 (48.3)	NS
Ovarian dysfunction	9 (2.4)	2 (1.2)	NS	2 (2.6)	NS	0	na ^d
Uterine factors	8 (2.1)	2 (1.2)	NS	1 (1.3)	na	1 (3.4)	na
Endometriosis	43 (11.3)	33 (20.2)	0.007	15 (19.7)	0.028	5 (17.3)	NS
Male factor	65 (17.1)	17 (10.4)	0.044	10 (13.2)	NS	5 (17.2)	NS
Unexplained	31 (8.1)	21 (12.9)	NS	11 (14.5)	NS	4 (13.8)	NS
No. of previous attempts	1.66 ± 0.10	1.33 ± 0.14	0.056	1.28 ± 0.20	NS	0.93 ± 0.21	0.002
Serum LH (mIU/ml)	4.32 ± 0.16	4.04 ± 0.14	NS	4.16 ± 0.20	NS	4.46 ± 0.31	NS
Serum E ₂ (pg/ml)	1555 ± 37	1758 ± 52	0.002	1745 ± 72	0.019	1682 ± 109	NS
No. of embryos transferred	3.64 ± 0.11	4.37 ± 0.14	<0.001	4.59 ± 0.20	<0.001	5.31 ± 0.30	<0.001
No. 1-cell excellent-good	0.21 ± 0.03	0.16 ± 0.03	NS	0.17 ± 0.05	NS	0.34 ± 0.10	NS
No. 1-cell poor	0.28 ± 0.03	0.22 ± 0.04	NS	0.18 ± 0.05	NS	0.21 ± 0.09	NS
No. 2-cell excellent	0.10 ± 0.02	0.11 ± 0.03	NS	0.09 ± 0.04	NS	0.17 ± 0.09	NS
No. 2-cell good	1.12 ± 0.06	1.44 ± 0.11	0.011	1.54 ± 0.17	0.02	1.93 ± 0.31	0.01
No. 2-cell poor	0.22 ± 0.03	0.12 ± 0.04	0.046	0.09 ± 0.04	0.009	2	na
No. 3-cell excellent-good	0.39 ± 0.03	0.58 ± 0.06	0.005	0.16 ± 0.10	0.035	0.51 ± 0.17	NS
No. 3-cell poor	0.06 ± 0.01	0.09 ± 0.03	NS	0.04 ± 0.03	NS	2	na
No. 4-cell excellent	0.13 ± 0.02	0.23 ± 0.05	NS	0.28 ± 0.08	NS	0.24 ± 0.13	NS
No. 4-cell good	0.88 ± 0.06	1.20 ± 0.10	0.006	1.39 ± 0.15	0.002	1.69 ± 0.24	0.001
No. 4-cell poor	0.09 ± 0.02	0.07 ± 0.02	NS	0.10 ± 0.04	NS	2	na
No. 5-cell all	0.14 ± 0.02	0.13 ± 0.03	NS	0.09 ± 0.03	NS	0	na
Donor sperm	27 (7.1)	15 (9.1)	NS	9 (11.8)	NS	2 (6.9)	NS
Transfer catheter: flexible	333 (87.6)	151 (92.0)	NS	70 (92.1)	NS	28 (96.5)	NS

^a Percentages in parentheses.^b Means ± SE.^c Nonsignificant.^d Nonapplicable.

3-, and 4-cell stages were significantly linked with successful IVF outcome, while transfer of 2-cell stage, poor-quality embryos was associated with IVF failure (Table I).

Multiple Regression Analysis

Because many of the variables in Table I are interrelated, a multiple logistic regression analysis was used to examine the variations observed by the univariate analysis. Dependent variables were pregnancies, live births, or multiple births and IVF failure. Additional variables that are not presented in Table I were examined: sperm parameters (concentration, percentage motility, and rate of progression) before and after standard Percoll processing, sperm concentration at insemination, number and quality of retrieved oocytes, and the "human" factor that may have resulted from different embryologists and physicians being involved at the time of oocyte retrieval and embryo transfer. Testing the above variables in initial models did not reveal any significant correlations. In addition, the number and quality of oocytes showed a strong correlation with the number and quality of embryos. The former were therefore rejected during the

regression analysis, and in the final models we used only the embryo variables.

Results of the logistic regression are presented in Table II. Endometriosis without tubal occlusion ($P = 0.04$) was positively correlated with pregnancy, whereas other causes of infertility were not. With respect to embryo characteristics 2-cell good-quality ($P = 0.001$), 3-cell excellent/good-quality ($P = 0.003$), 4-cell excellent-quality ($P = 0.002$), and 4-cell good-quality ($P = 0.02$) transferred embryos were positively associated with pregnancy. The same group of good-quality embryos showed a significant correlation with live births, as well as pregnancies. In addition, the use of donor sperm ($P = 0.03$) proved to be positively correlated with live births. Maternal age was negatively correlated ($P = 0.02$). Multiple births were significantly correlated only with 2-cell good-quality ($P = 0.0002$), 4-cell excellent-quality ($P = 0.002$) and 4-cell good-quality ($P = 0.0002$) embryos.

Estimation of Probabilities for IVF Outcome

Multivariate analysis indicated that good-quality embryos were positively correlated with live births,

Table II. Coefficient (Coeff.) and *P* Value for Each Characteristic After the Logistic Regression

Characteristic	Pregnancy vs failure			Live births vs failure			Multiple births vs failure		
	Coeff.	SE	<i>P</i>	Coeff.	SE	<i>P</i>	Coeff.	SE	<i>P</i>
Age	-0.05	0.03	0.06	-0.08	0.03	0.02	-0.08	0.05	0.09
Tubal factor	0.97	0.87	0.26	-0.17	0.88	0.84	-0.69	0.89	0.44
Ovarian dysfunction ^a	0								
Uterine factors	0.01	1.22	0.12	0.46	1.23	0.71			
Endometriosis	1.85	0.90	0.04	0.49	0.91	0.59	-0.13	0.99	0.89
Male factor	0.66	0.91	0.47	0.16	0.93	0.87	0.05	0.98	0.96
Unexplained	1.43	0.91	0.12	0.33	0.93	0.72	-0.37	1.00	0.71
No. of previous attempts	-0.08	0.07	0.21	-0.06	0.09	0.51	-0.21	0.16	0.20
Serum LH	-0.03	0.05	0.54	-0.00	0.07	0.93	0.07	0.06	0.24
Serum E ₂	0.00	0.00	0.32	-0.00	0.00	0.56	-0.00	0.00	0.09
No. 1-cell excellent/good	-0.27	0.22	0.21	-0.11	0.28	0.70	0.56	0.31	0.07
No. 1-cell poor	-0.14	0.19	0.45	-0.16	0.26	0.55	0.12	0.37	0.75
No. 2-cell excellent	-0.05	0.26	0.86	0.33	0.41	0.42	0.52	0.41	0.21
No. 2-cell good	0.29	0.09	0.001	0.34	0.10	0.001	0.55	0.15	0.0002
No. 2-cell poor	-0.27	0.23	0.24	-0.31	0.37	0.41	-0.32	0.69	0.64
No. 3-cell excellent/good	0.41	0.14	0.003	0.41	0.17	0.02	0.37	0.29	0.19
No. 3-cell poor	0.31	0.28	0.27	-0.43	0.54	0.43	0.00	0.82	0.10
No. 4-cell excellent	0.71	0.23	0.002	1.00	0.26	0.0001	1.21	0.39	0.002
No. 4-cell good	0.22	0.09	0.02	0.34	0.12	0.005	0.66	0.18	0.0002
No. 4-cell poor	-0.17	0.29	0.55	0.22	0.32	0.51	0.15	0.59	0.81
No. 5-cell all	0.05	0.27	0.85	-0.21	0.42	0.62	na ^b		
Donor sperm	0.66	0.41	0.11	1.02	0.48	0.03	0.65	0.84	0.44
Transfer catheter: flexible	0.67	0.37	0.07	0.58	0.48	0.23	1.75	1.16	0.13

^a Ovarian dysfunction as reference for comparisons among causes for IVF.

^b Nonapplicable.

while maternal age was negatively correlated. Using these variables, we estimated the probabilities for live and multiple births for each patient's cycle. We also included age in the multiple-birth model, since its correlation coefficients for live and multiple births were similar.

The final equations were as follows.

Live birth

$$P_L = -0.49 - 0.074 \times \text{age} + 0.31 \times \text{2-cell good} \\ + 0.41 \times \text{3-cell good} + 0.84 \times \text{4-cell excellent} \\ + 0.38 \times \text{4-cell good}$$

Multiple births

$$P_M = -1.16 - 0.095 \times \text{age} \\ + 0.46 \times \text{2-cell good} + 0.81 \times \text{4-cell excellent} \\ + 0.51 \times \text{4-cell good}$$

For example, the probability of live birth for a 38-year-old woman receiving one 2-cell good and one 4-cell good embryo is

$$P_L = -0.49 - 0.074 \times 38 + 0.31 \times 1 + 0.38 \times 1 \\ = -2.612$$

$$P_L = 1/1 + e^{-P_1} = 1/1 + 2.718^{-(-2.612)} \\ = 1/1 + 13.62 = 0.068 \quad \text{or} \quad 6.8\%$$

The probability for multiple births is

$$P_M = -1.16 - 0.095 \times 38 + 0.46 \times 1 + 0.51 \times 1 \\ = -3.8$$

$$P_M = 1/1 + e^{-P_2} \\ = 1/1 + 2.718^{-(-3.8)} = 1/1 + 44.7 \\ = 0.022 \quad \text{or} \quad 2.2\%$$

Embryo Transfer Strategies

As is obvious from the final equations, good-quality embryos have different odds for live or multiple births at different maternal ages. This allows us to test in mathematical models the hypothesis that increasing the number of good-quality embryos transferred as maternal age advances may maintain the same odds of live birth as for younger ages, without a further increase in the odds of multiple births. Within this context, using the final equations given above, we calculated the odds for live and multiple births for

Fig. 1. The ratio of the probability for live births to the probability for multiple births as a function of the number of good-quality embryos transferred at different maternal ages.

each type of good-quality embryo as a function of increasing number of embryos transferred and maternal age expressed as 5-year incremental increases between 25 and 45 years.

Figure 1a depicts the ratio of the probability of 2-cell good embryos for live birth to the probability for multiple births as a function of the number of such embryos transferred at different maternal ages. Figures 1b and c present the same correlations for 4-cell good and 4-cell excellent embryos, respectively. It is apparent that the odds for live births over multiple births for any given number of transferred embryos are dependent on the maternal age. As the maternal age increases, transfer of the same number of good-quality embryos results in lower odds of multiple births relative to the odds for live birth. In contrast, the ratio of live to multiple births can be maintained at the same level by transferring one more embryo of good quality for approximately every 5-year incremental increase in maternal age. However, transfer of more embryos increases the chances for live birth. For example, transfer of two 4-cell good embryos in a woman 30 years old gives 12.5% chances for a live birth and 2.6% for a multiple birth. In a 35-year-old woman these odds, 12.6% for a live birth and 2.5% for a multiple birth, can be expected with three 4-cell good-quality embryos. In a 40-year-old, these odds are 12.6 and 2.5%, respectively, with 4 of these embryos, and in a 45-year-old, these rates are 12.8 and 2.4%, respectively, with 5 embryos. Such a strategy may keep the chances for live birth relatively constant as maternal age advances without further increasing the multiple birth rate.

DISCUSSION

This study was initiated to identify factors that can significantly influence IVF outcome. The method used

was a multivariate analysis to minimize the effects of interrelationships among such factors. Furthermore, analysis of all patients undergoing IVF during a given period by the same stimulation protocol decreases the multiple confounding effects of different regimens on ovarian and endometrial physiology. An attempt to quantitate those factors was made using logistic regression. This approach was undertaken not only to estimate the probabilities that a certain couple in a given IVF cycle will have a live birth or multiple birth, but also to explore strategies that might improve IVF outcome, balancing factors that have positive and negative effects on IVF success.

Maternal age was the most significant negative factor in IVF success. Data from IVF registries support this finding (3,4). The age effect was more prominent in the live birth rate. This probably reflects the fact that even when implantation is achieved, a higher spontaneous abortion rate in older women will result in a lower birth rate. Previous studies addressed the relation of spontaneous abortion rate to advanced maternal age, pointing to the fact that the age of the oocyte is most highly correlated with the age-related increase in spontaneous abortion rates and the decrease in live birth rates (10). In our study, after correction for many variables related to IVF success, maternal age emerged as an independent negative predictor for live births after IVF, whereas it was not a strong predictor for implantation. This features points to an age-related fetal wastage in the IVF procedure.

Patients with endometriosis without tubal occlusion as a single factor for IVF had a higher probability of achieving implantation. This factor did not maintain its significance when live birth rates were considered. It can be postulated that endometriosis at that level may not interfere with implantation but, thereafter, may increase the chances of spontaneous abortion. Therefore, the increment in pregnancy rate does not

lead to an increase in live births. The role of endometriosis in the spontaneous abortion rate in the infertile and IVF population is not clear. Some studies suggested that endometriosis can be associated with increased spontaneous abortion rates and that treatment of endometriosis with long-term GnRH agonists before IVF decreases the rate of spontaneous abortions (11–13). However, most studies lack appropriate controls and power (14). In our study many factors that can influence IVF outcome, particularly the quality of transferred embryos, were taken into account; therefore, endometriosis without tubal blockage, as a single factor for infertility, represents a favorable characteristic for successful implantation. However, this does not translate into an increase in the birth rate. These results suggest that endometriosis in patients undergoing IVF may increase the spontaneous abortion rate. Further investigation of the role of endometriosis in early pregnancy should be considered.

The diagnosis of male factor in terms of concentration, motility, and morphology of sperm has been shown to influence IVF outcome (1–5). In our study patients with total failed fertilization were excluded and donor insemination treatment cycles were classified separately. Univariate analysis showed a negative effect of male factor on pregnancy rate, probably reflecting a low fertilization rate. In contrast, multivariate analysis showed that in those couples, once they achieved embryo transfer, male factor was not a significant variable in IVF outcome. In contrast, donor insemination proved to be an effective treatment since it significantly improved birth rates. In the multivariate analysis, the lack of significance of donor sperm treatment on pregnancy rates in the face of a significant correlation with live birth rates implies that donor sperm results in a lower spontaneous abortion rate. These results suggest a potential role for sperm after fertilization in implantation and early fetal–maternal unit function.

It is clear that the number and quality of embryos are the critical determinants of IVF success. In this study we attempted to evaluate the potential for implantation, live births, and multiple births of each embryo according to the morphologic quality and the number of blastomeres. Our data demonstrated that IVF-derived embryos have different potentials for implantation, live births, and multiple births. Embryos of poor quality in any developmental stage as well as any 1-cell-stage embryo did not contribute significantly to IVF success. Only 2-, 3-, and 4-cell good-quality embryos are associated with implantation and deliveries. These embryos also demon-

strated different strengths of their correlations with IVF outcome. The 4-cell, excellent embryo seems to be the embryo most likely to result in a live birth. These results were obtained by logistic regression and therefore were adjusted for maternal age and all the other variables examined. Similar data from Acosta *et al.* (15), Staessen *et al.* (16), and Shulman *et al.* (7) using univariate analysis suggested that the implantation potential of each embryo is different and pregnancy rate is correlated with good-quality transferred embryos. These data raise questions of how embryos of poor quality should be utilized after an IVF cycle.

Another feature of good-quality embryos is that they also presented different potentials for multiple births. Again, 4-cell excellent embryos seem to be most strongly associated with multiple births. It is noteworthy that 3-cell good-quality embryos do not correlate with multiple births. It is likely that this is a result of the low number of 3-cell good embryos transferred in the group with multiple births. The fact that embryos have different potentials for live and multiple births at different patient ages suggests the hypothesis that transfer of more good-quality embryos as the woman's age advances will maintain the odds for live births without a concomitant increment in multiple births. As presented in Fig. 1, this can be achieved by transferring one more good-quality embryo for each approximately 5-year incremental increase in maternal age. Using the equations derived from the logistic regression, the odds for live and multiple births can be calculated for each patient according to the available good-quality embryos, thereby choosing the set of embryos that will provide the best odds for this attempt. Our results suggest that this approach can be tested in a prospective way. In addition, during IVF treatment efforts must be directed toward increasing the number of good-quality embryos.

In summary, multivariate analysis of several epidemiological, stimulation cycle, and embryo characteristics of patients undergoing IVF revealed that only maternal age negatively influences live birth rates, whereas good-quality embryos positively influence this rate. Furthermore, each good-quality embryo has a different potential for live and multiple births. Based on these results, modification of the transfer strategy by transferring one more good quality embryo for each approximately 5-year incremental increase in maternal age, after the age of 30, should maintain the odds for babies as maternal age

advances without a concomitant increment in multiple births.

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