Predictors of treatment failure in young patients undergoing in vitro fertilization

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Abstract

Purpose The purpose of the study was to evaluate whether routinely collected clinical factors can predict in vitro fertilization (IVF) failure among young, “good prognosis” patients predominantly with secondary infertility who are less than 35 years of age. **Methods** Using de-identified clinic records, 414 women <35 years undergoing their first autologous IVF cycle were identified. Logistic regression was used to identify patient-driven clinical factors routinely collected during fertility treatment that could be used to model predicted probability of cycle failure. **Results** One hundred ninety-seven patients with both primary and secondary infertility had a failed IVF cycle, and 217 with secondary infertility had a successful live birth. None of the women with primary infertility had a successful live birth. The significant predictors for IVF cycle failure among young patients were fewer previous live births, history of biochemical pregnancies or spontaneous abortions, lower baseline antral follicle

count, higher total gonadotropin dose, unknown infertility diagnosis, and lack of at least one fair to good quality embryo. The full model showed good predictive value ($c=0.885$) for estimating risk of cycle failure; at $\geq 80\%$ predicted probability of failure, sensitivity = 55.4 %, specificity = 97.5 %, positive predictive value = 95.4 %, and negative predictive value = 69.8 %.

Conclusion If this predictive model is validated in future studies, it could be beneficial for predicting IVF failure in good prognosis women under the age of 35 years.

Keywords IVF · Young patients · Cycle failure · Early clinical factors · Predictors

Capsule If this predictive model is validated in future studies, it could be beneficial for predicting IVF failure in good prognosis women under the age of 35 years.

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Introduction

A vast amount of research has been published regarding poor prognosis patients over the age of 35 years undergoing in vitro fertilization (IVF); however, little research has focused on young, “good prognosis” patients. This is important as young patients undergoing IVF are often reassured of their good prognosis and are therefore more surprised than older women when they do not achieve a live birth following treatment, though more than half of these patients are likely to fail [1]. These unrealistic expectations of success may lead to increased psychological distress following a failed treatment cycle [2, 3] and may leave both the clinician and patient wondering whether this failure could have been predicted earlier.

Most studies that consider treatment failure among young women have examined young poor responder (PR) patients, defined as patients with suboptimal follicular development and low estradiol (E_2) levels following ovarian hyperstimulation [4–7]. Findings from these studies suggest similar implantation and pregnancy rates in young PR patients and young patients who respond normally to treatment [4, 6], as

well as significantly higher clinical pregnancy rates in young PR patients than older women [7]. Additional investigations undertaken among young patients with high order recurrent implantation failure (failure to achieve a pregnancy following ≥ 6 consecutive IVF cycles) found that compared to women who achieved a pregnancy within the first three cycles, male characteristics, such as the presence of male-factor infertility and low semen concentration, were the primary drivers of recurrent implantation failure [8]. Thus, in general, these findings support higher expected success rates among younger women and do not explain why some women in this age group, most of whom are probably not poor responders or undergoing repeated IVF cycles, fail to achieve a pregnancy.

The goal of the present study was to evaluate clinical variables routinely collected prior to embryo transfer that may be associated with cycle failure among young women undergoing IVF.

Methods

A retrospective review (2006–2011) of de-identified patient records was conducted to identify women under the age of 35 years undergoing their first fresh IVF cycle at Reproductive Partners Medical Group - UCSD Regional Fertility Center in La Jolla, CA ($n=479$). This 6-year study period was defined a priori, reflecting 2006 as the start of electronic data capture at this clinic and 2011 as the last year that complete data was available at the time of data extraction. Donor-recipient cycles were excluded due to small numbers ($n=16$). Patients with ongoing pregnancies at the time of data extraction ($n=42$) were removed as pregnancy outcome was unknown. After excluding two patients who elected to forego embryo transfer due to personal reasons, and five patients who underwent IVF for embryo banking, 414 women remained for inclusion in the study. Of these, only 9.2 % of these women had primary infertility. No selection was made on infertility type or reproductive background; thus, this population represents the population of women under the age of 35 years who initiated a cycle at this clinic.

Although no patient identifiers were used, the study received Institutional Review Board approval from the University of California, San Diego Human Research Protection Program.

Measures

At cycle initiation, a number of clinical factors were recorded, including patient age in years, smoking status (yes/no), and height and weight, which were used to calculate body mass index (BMI; kg/m^2). Reproductive history variables included the number of previous pregnancies, live births, spontaneous abortions, biochemical pregnancies (a positive pregnancy test that did not progress to the development of a fetal heartbeat),

and intrauterine insemination (IUI) attempts. A clinical judgment of infertility diagnosis was made following diagnostic categories defined by the Society for Assisted Reproductive Technology (SART) [9]. A blood draw was conducted on day 3 of the patient's menstrual cycle to determine baseline follicle-stimulating hormone (FSH) level, and a transvaginal ultrasound was conducted to determine antral follicle count (AFC), the number of antral follicles observed in both ovaries.

All patients underwent controlled ovarian hyperstimulation, consisting of standard GnRH downregulation followed by hMG (75 IU) and recombinant FSH (75–300 IU); gonadotropin dose was determined individually depending on patient age, weight, anti-Müllerian hormone level, FSH, and AFC. Daily estradiol (E_2) level was monitored via blood draw from day 3 of stimulation until egg retrieval; maximum E_2 was the highest level measured. Total gonadotropin dose and number of stimulation days were recorded. Human chorionic gonadotropin (hCG) was administered when ≥ 2 follicles reached a mean diameter of 18 mm. Number of follicles greater than 14 mm observed via ultrasound and E_2 on the day of the hCG trigger were assessed. Oocyte recovery was performed 35 h after hCG administration, and standard insemination or ICSI was performed as clinically appropriate. Luteal support, initiated the day following oocyte recovery, consisted of 50 mg IM progesterone in oil and 4 mg estradiol administered orally and continued through 10 weeks gestation in women who became pregnant.

Embryos were transferred on day 3 (cleavage stage) for patients who did not meet criteria for extended culture (4+ embryos on day 3, at least 3 being 8-cell of “fair” to “good” quality). Embryos graded as “good” had at least seven cells, and ≤ 10 % fragmentation with perfect cell symmetry or 0 % fragmentation with moderate symmetry. Embryos ≤ 5 cells, with >25 % fragmentation, and severely uneven cell symmetry were graded as “poor,” as were embryos with 11–25 % fragmentation and moderate symmetry. Blastocysts (day 5 transfers) were graded as good if the inner cell mass consisted of many, tightly packed cells, and the trophoblast was comprised of many cells forming a cohesive epithelium, or a few cells forming a loose epithelium [10]. Blastocysts with very few cells in either the inner cell mass or the trophoblast, early blastocysts with no inner cell mass and trophoblast, and morula stage embryos were graded as poor.

Statistical analysis

The outcome of interest in the present study was a failed IVF cycle, defined as failure to achieve a live birth following an initiated IVF cycle; a “successful” IVF cycle was defined as a cycle resulting in a live birth.

Cause of infertility was condensed to reflect the partner's primary infertility diagnosis (i.e., female factor, male factor, or unexplained/other). Female diagnoses included the following:

diminished ovarian reserve, endometriosis, ovulation disorders/polycystic ovarian syndrome, tubal disease, and uterine factors; and male factor infertility is a pre-specified SART diagnostic category. The initial approach was to evaluate all female fertility etiologies separately; however, the paucity of data in some diagnostic categories did not permit isolated analysis. Previous studies have shown similar effects on IVF success for all female etiologies [11, 12], leading some researchers to group prediction models into groups of “known etiology” versus idiopathic [12, 13]. Patients who did not fit into any of the pre-defined SART diagnoses, or for whom infertility etiology could not be determined, were considered unexplained/other. Few patients had both male and female factors listed ($n=39$), and inclusion of these patients as a separate category (i.e., both male and female) did not increase model fit.

Because of the difficulty in accurately recalling spontaneous abortions and biochemical pregnancies, especially those that terminate early on [14–16], and since very few patients reported more than one of each, history of spontaneous abortions and biochemical pregnancies was dichotomized as ≥ 1 versus none. AFC and number of follicles >14 mm were highly skewed and were therefore classified into tertiles. Fertilization rate was defined as the number of oocytes fertilized divided by the number inseminated. Embryo quality was categorized as at least one fair to good grade embryo versus none.

Logistic regression was used to determine predictors of IVF cycle failure. All variables that differed between patients with successful versus failed IVF cycles at $p \leq 0.15$ were considered for inclusion in predictive models. Model building began by first including variables significant at $p < 0.001$, then $p < 0.01$, $p < 0.05$, and finally, $p \leq 0.15$. At each step, variables significant at $p \leq 0.15$ were retained. Less than 10 % of patients were missing data for all variables considered. The Hosmer-Lemeshow goodness-of-fit statistic was used to evaluate the fit of the model, with $p > 0.10$ necessary to conclude acceptable fit. Due to the large number of patients with a prior live birth, model building was repeated among parous women only ($n=301$). The predictive ability of the final model was evaluated using the c-statistic, an estimate of the AUROC which calculates the probability of a correct prediction for a random pair of patients, one of whom has the outcome and one who does not. Predictive ability was validated using bootstrapping of 100 replicate iterations of unrestricted randomly resampled data [17]. Analyses were conducted using SAS 9.3.

Results

Overall, 197 patients (47.6 %) had a failed IVF cycle and 217 (52.4 %) had a successful live birth (Table 1). Average age

was 31.4 years (SD=2.5, range 19–34); and those with a failed cycle were slightly older. Patients who failed to achieve a live birth reported fewer prior pregnancies and live births and were more likely to report spontaneous abortions and biochemical pregnancies. Women with a failed cycle had higher baseline FSH, had lower maximum E_2 , and required a higher gonadotropin dose. They were also more likely to be in the lowest tertiles for AFC and number of follicles >14 mm and have no fair to good embryos. As all women who initiated an IVF cycle were included in the present population and not all women progressed to embryo transfer (considered a failed cycle), only factors leading up to embryo transfer were considered. However, among those who progressed to embryo transfer, the mean number of embryos transferred was 1.81 (SD=0.49, range 0–4); no differences were noted by group (failure 1.82 vs. success 1.78, $p=0.39$).

Higher number of previous live births decreased odds of failure (aOR=0.11, 95 % CI 0.07–0.17 for each additional live birth), while history of biochemical pregnancies or spontaneous abortions increased odds of failure (aOR=3.30, 95 % CI 1.31–8.36 and aOR=3.54, 95 % CI=1.93–6.49, respectively) (Table 2). Those in the lowest tertile for AFC had higher odds of failure compared to those in the highest tertile (aOR=2.87, 95 % CI 1.43–5.76), as did patients with no fair to good embryos (aOR=3.50, 95 % CI 2.01–6.08) and those requiring a higher gonadotropin dose (aOR=1.04, 95 % CI 1.02–1.06 for a 100-unit increase in dose). Compared to patients with unexplained fertility, female factor infertility diagnosis decreased odds of failure (OR=0.40, 95 % CI 0.21–0.76). The model showed good predictive value ($c=0.885$); bootstrapping analysis of the final model yielded similar results ($c=0.891$, 95 % CI 0.852–0.917).

Among parous women, similar variables were identified, though embryo quality fell out of the model (Table 3). Additionally, the impact of number of previous live births was only marginally significant, as might be expected given all women had at least one. Other estimates were not materially different. Predictive ability of the model was reasonable, though slightly lower ($c=0.752$).

The beta coefficients presented in Table 2 were used to calculate probability of failure for each patient in the database who had all relevant clinical measures ($n=383$). Proportion of patients with a failed cycle increased as predicted probability of failure increased (Table 4). Among patients who had ≥ 80 % predicted probability of failure, 95.4 % experienced a failed cycle (103/108), equating to a positive predictive value of 95 %. At this cut-point, slightly more than half of the patients who had a failed cycle were screened out (sensitivity=103/186, 55.4 %). Specificity was very high, correctly identifying 97.5 % of young women who ultimately had a successful IVF cycle (192/197), though negative predictive value was lower (192/275=69.8 %).

Table 1 Clinical characteristics of the study sample by IVF outcome

Clinical factor	Overall <i>N</i> = 414	IVF failure (no live birth) <i>n</i> = 197	IVF success (live birth) <i>n</i> = 217	<i>p</i> value ^a
Patient age (years), mean	31.4	31.7	31.1	0.007
(Range)	(19–34)	(24–34)	(19–34)	
BMI (kg/m ²), mean	23.0	23.2	22.8	0.26
(Range)	(16–41)	(16–41)	(16–36)	
Number of pregnancies, mean	1.7	1.5	2.0	<0.001
(Range)	(0–7)	(0–6)	(1–7)	
Number of live births, mean	0.9	0.5	1.3	<0.001
(Range)	(0–4)	(0–4)	(1–4)	
Previous SAB, % yes	31.4	40.6	23.0	<0.001
Previous biochemical, % yes	10.9	16.2	6.0	0.001
Previous IUI, % yes	8.0	7.6	8.3	0.80
Infertility diagnosis, percent				0.10
Female primary	45.9	43.6	48.2	
Male primary	31.9	29.6	34.0	
Unexplained/other	22.2	26.9	17.8	
Day 3 FSH (mIU/mL), mean	8.0	8.6	7.4	0.01
Antral follicle count (%)				<0.001
Tertile 1 (<5)	33.1	39.6	27.2	
Tertile 2 (5–19)	35.5	37.6	33.6	
Tertile 3 (≥20)	31.4	22.8	39.2	
Maximum E ₂ (pg/mL), mean	2462.6	2297.4	2615.6	0.02
E ₂ day of hCG (pg/mL), mean	2479.8	2481.8	2478.2	0.98
Gonadotropin dose (IU), mean	2348.1	2685.3	2037.8	<0.001
Num. stimulation days, mean	9.0	9.3	8.8	0.05
Num. follicles >14 mm (%)				0.005
Tertile 1 (<2)	28.5	36.1	21.7	
Tertile 2 (2–3)	32.1	28.9	35.0	
Tertile 3 (>3)	39.4	35.0	43.3	
Num. retrieved oocytes, mean	14.2	13.9	14.4	0.50
Fertilization rate, mean	75.4	72.8	77.4	0.05
Embryo grades				<0.001
All embryos poor	59.2	69.0	50.2	
At least one fair embryo	40.8	31.0	49.8	

SAB spontaneous abortion, IUI intrauterine insemination, FSH follicle-stimulating hormone, E₂ estradiol, hCG human chorionic gonadotropin

^a *p* value calculated using chi-square analysis for categorical variables and independent *t* tests for continuous variables

Discussion

To our knowledge, this study is the first to model predictors of failure among young women predominantly with secondary infertility undergoing IVF. The most relevant early predictors of cycle failure for women under 35 years of age were comprehensive reproductive history, infertility diagnosis, ovarian reserve, gonadotropin dose, and embryo quality. These factors, in combination, provided a good predictive estimate of failure, as suggested by the high failure rate among patients with a predicted failure rate of ≥80 %. Reproductive history accounted for approximately 28 % of the variance in outcome,

while the remaining clinical factors explained 13 %, based on *r*-squared estimates of the final model. While these findings are not necessarily unique within the scope of fertility treatment, they do suggest that even among women expected to have a good prognosis, a clinical profile of those at high risk for failure can be developed.

Findings from the present investigation may be important as the field continues to move towards stronger recommendations for elective single embryo transfer (eSET), as the present study population represents women who would currently be targeted for elective single embryo transfer under existing guidelines. Current guidelines in the USA, UK, and Canada

Table 2 Clinical factors associated with IVF failure in young women

Characteristic	β	aOR ^a	95 % CI
Number of previous live births	−2.2539	0.11	0.07–0.17
History of biochemical pregnancies	1.1950	3.30	1.31–8.36
History of spontaneous abortions	1.2644	3.54	1.93–6.49
Primary infertility diagnosis			
Female	−0.9155	0.40	0.21–0.76
Male	−0.4706	0.63	0.32–1.20
Unexplained/other	–	Ref	–
Antral follicle count			
Tertile 1 (<5)	1.0554	2.87	1.43–5.76
Tertile 2 (5–19)	0.2170	1.24	0.62–2.48
Tertile 3 (≥20)	–	Ref.	–
Gonadotropin dose	0.0004	1.04 ^b	1.02–1.06
No fair or good embryos	1.2516	3.50	2.01–6.08

Results of logistic regression; $c = 0.885$ ^a Odds ratios adjusted for all other variables in the table; for continuous variables, odds ratio represents change for a 1-unit increase, unless otherwise stated^b OR for a 100-unit increase

highlight consideration of eSET in young patients (<35 USA, ≤37 Canada, UK) undergoing their first IVF cycle with top-quality embryos available [18–20]. While results of the present study support higher expected success rates among young patients with at least one high-quality embryo, they also suggest additional considerations may be important in this population. Though poor embryo quality, frequently related to advanced maternal age, has been previously linked to IVF

Table 3 Clinical factors associated with IVF failure in young, parous women

Characteristic	β	aOR ^a	95 % CI
Number of previous live births	−0.5387	0.58	0.34–1.01
History of biochemical pregnancies	1.3538	3.87	1.51–9.97
History of spontaneous abortions	0.9077	2.47	2.31–4.68
Primary infertility diagnosis			
Female	−0.9306	0.39	0.19–0.82
Male	−0.4285	0.65	0.31–1.39
Unexplained/other	–	Ref.	–
Antral follicle count			
Tertile 1 (<5)	1.2164	3.37	1.61–7.08
Tertile 2 (5–19)	0.2846	1.33	0.61–2.90
Tertile 3 (≥20)	–	Ref.	–
Gonadotropin dose	0.0003	1.03 ^b	1.00–1.05

Results of logistic regression; $c = 0.752$ ^a Odds ratios adjusted for all other variables in the table; for continuous variables, odds ratio represents change for a 1-unit increase, unless otherwise stated^b OR for a 100-unit increase**Table 4** Predicted probabilities of failure and actual IVF outcome in the current sample

IVF cycle outcome	Predicted probability of failure					Total
	<20 %	20–39 %	40–59 %	60–79 %	≥80 %	
Cycle failure, no live birth (<i>n</i>)	11	19	22	31	103	186
Cycle success, live birth (<i>n</i>)	104	43	35	10	5	197
Total (<i>n</i>)	115	62	57	41	108	383

failure [13, 21–23], embryo quality accounted for little variance in the present study (~4 %) and fell out of final models when parous women only were considered. Detailed reproductive history, infertility diagnosis, AFC, and gonadotropin dose all contributed significant additional information regarding the likelihood of cycle failure among women in the present investigation, who were all young and undergoing their first known IVF cycle. Current recommendations do not discuss reproductive history, yet none of the women with primary infertility ($n = 38$) in the present study had a successful live birth. Thus, results suggest that additional considerations may be warranted when characterizing good prognosis patients to recommend eSET, which may, in turn, lead to higher success rates following the procedure. Further, acceptability of eSET may increase if patients feel they have been more thoroughly characterized as a good prognosis patient, and perception of control over one's treatment options has been shown to decrease fertility-related stress and anxiety following IVF [2].

While a number of early clinical factors were considered in the present study, we were unable to examine lifestyle characteristics such as smoking, alcohol intake, and caffeine consumption [24, 25], or patient characteristics such as ethnicity [26]. Additionally, grouping female diagnoses into one category has many drawbacks; various infertility etiologies affect female fertility in distinct ways, and consideration of all etiologies together does not address this. Larger future studies may also allow for differentiation among female diagnostic categories. A major strength of this study was the availability of patient-level rather than cycle-level data, which eliminated confounding from interrelated cycles from the same patient being considered. Thus, all data used provided distinct information to the model and allowed individual patient profiles to be evaluated.

While it would be extremely premature to make any clinical recommendations, data from this study, if confirmed in future studies, may provide useful knowledge for reproductive endocrinologists as they advise patients with secondary infertility less than 35 years of age when guiding them through the IVF process. Many of the factors identified are not currently modifiable by the infertility patient; however, future research into possible ways of enhancing embryo quality, increasing ovarian reserve, and decreasing gonadotropin levels may be relevant to young infertile women, as suggested by our

findings. Emerging research suggests that supplementation with dehydroepiandrosterone (for increasing ovarian reserve and enhancing embryo and oocyte quality), melatonin (for enhancing oocyte and embryo quality), or myo-inositol (for increasing oocyte quality and decreasing gonadotropin dose) may help improve these factors [27–30], though more research is needed.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Conflict of interest The authors declare that they have no conflict of interest.

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