Point of failure as a predictor of in vitro fertilization treatment discontinuation

Among 2,245 women, those who experienced a chemical pregnancy that failed to progress to a clinically recognized pregnancy or a spontaneous abortion on their first IVF cycle were more likely to discontinue IVF treatment than those whose first cycle ended before embryo transfer or who did not have a positive pregnancy test after transfer. However, among women who did continue to a second IVF cycle, those who had at least a chemical pregnancy on the first cycle were more likely to have a live birth on the second attempt than those women who had failed before conception in the first cycle (34% success rate compared with 21%, respectively). (Fertil Steril® 2009;91:1483–5. ©2009 by American Society for Reproductive Medicine.)

Since its advent three decades ago, in vitro fertilization (IVF) has become a commonly used assisted reproductive technology (ART) (1). Success rates have increased, and such procedures are covered by some medical insurance plans in the United States. However, the IVF process remains a difficult one—physically, emotionally, and financially—for the subfertile couple, and most do not succeed on the first attempt. Furthermore, eventual success is not guaranteed, even for those couples willing to attempt repeated cycles. These difficulties cause many couples to cease IVF treatment before a successful birth. Several studies have explored reasons for dropout, including psychologic burden, poor prognosis, financial burden, and spontaneous pregnancy (2–7). De Vries et al. (8) and Sharma et al. (9) investigated the relation between dropout and characteristics of the previous cycles, such as number of oocytes retrieved or fertilization rate. Using data from a large multicenter IVF study, we explored the relationship between treatment discontinuation and the outcome of the woman's last IVF cycle.

Married couples newly enrolled for ART treatment between 1994 and 1998 (first study enrollment phase) and between 1999 and 2003 (second enrollment phase) at three clinics in the Boston area were eligible to participate in the study. Those using donor gametes or gestational carriers were not eligible. Enrolled couples completed baseline questionnaires and consent forms; the study was approved by the Brigham and Women's Hospital and Harvard School of Public Health Institutional Review Boards. Information on the couples' infertility history and diagnoses were abstracted from medical records, as were ART treatment details. For IVF cycles, these details included, e.g., use of down-regulation, method of insemination, number of oocytes retrieved, fertilization rate, number of embryos transfered, and ultimate outcome of the cycle.

The original study population included 2,687 couples undergoing ART for up to six cycles. Those whose treatment included the use of donor gametes were ineligible. Non-IVF cycles (such as gamete intrafallopian tube transfer [GIFT] or cryoembryonic transfer [CET] cycles) were excluded from this subanalysis. After additionally excluding 364 women with previous IVF history, 50 with no IVF cycles, 9 with no known IVF outcomes, and 19 missing covariate information, the analytic data set consisted of information on 2,245 women. The average age of these women was 35.2 years (SD 4.3, range 20–49), and 20% were parous. Infertility was diagnosed as primarily female-related in 34% and primarily male-related in 32% of couples; the remaining infertility was diagnosed as idiopathic.

The outcome of each IVF cycle was categorized as one of the following seven types: no retrieval (cancelation after initiating medication: 8% cycle 1, 8% cycle 2), failed fertilization (poor oocyte quality, poor semen, or no embryos created: 6% cycle 1, 6% cycle 2), all embryos frozen (3% cycle 1, 2% cycle 2), failed implantation (i.e., at least one embryo was transfered to the uterus but no pregnancy was detected on β-hCG test: 42% cycle 1, 49% cycle 2), chemical pregnancy only (positive β-hCG test but no uterine gestational sac detected on ultrasound [includes ectopic pregnancies]: 8% cycle 1, 7% cycle 2), pregnancy loss (spontaneous abortion, therapeutic abortion or stillbirth: 5% cycle 1, 5% cycle 2), or live birth (28% cycle 1, 23% cycle 2).

A couple was considered to have discontinued treatment if they did not return for further IVF after a failed IVF attempt. However, cycles ending in freezing all embryos presented difficulties in that it was unclear (owing to the lack of data on CET cycles) whether or not the cycle ultimately culminated in a successful live birth. For this reason, subjects were excluded from the analysis after such a cycle.

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On the first IVF cycle, 618 women (28%) had a live birth and 68 (3%) froze all embryos. Of the remaining 1,559 women, 373 (24%) ceased IVF treatment and 1,186 (76%) continued. Of these 1,186 second IVF cycles, 276 (23%) resulted in a live birth and 17 (1%) froze all embryos. Of the remaining 893 women, 314 (35%) discontinued treatment and 579 (65%) underwent a third IVF attempt. Logistic regression was performed to evaluate the association between first cycle outcome (categorized as described in the preceding paragraph) and the likelihood of discontinuing treatment after the first cycle. The analysis was repeated for the association of the second cycle outcome and the likelihood of discontinuing treatment after the second cycle. Both models included maternal age (categorized as $\leq$34 yrs, 35–39 yrs, or $\geq$40 yrs) and parity (yes/no), and also controlled for study site (1, 2, or 3), and study phase (1994–1998 or 1999–2003). Owing to sparse numbers, the likelihood of dropout after cycle 3 and beyond was not analyzed.

Women attaining only a chemical pregnancy or a clinical pregnancy that did not result in live birth on the first IVF cycle were more likely to discontinue treatment, but this association did not carry over to the second cycle (Table 1). An association of older female age and higher likelihood of dropout was seen at cycle two, but not cycle one. Of predictors considered, only parity was found to be associated with treatment cessation across IVF attempt number: Women who had previously given birth were much less likely to continue IVF treatment.

Additional variables (such as diagnosis group) were considered but were not statistically significant predictors in univariate models, nor did their inclusion change the observed associations or significance levels of other covariates in the multivariate models. We also considered including the outcomes of both cycles 1 and 2 as predictors for dropout after cycle 2, but doing so did not improve model fit. Although midcycle variables (such as number of oocytes retrieved) have been shown to be predictive of dropout (9), we did not include these variables as risk factors in the model, because we wanted to include women whose cycles failed early (for whom such midcycle variables do not exist, e.g., no oocyte retrieval) in the analysis. When the analysis was repeated restricted only to data from cycles where at least one embryo was transfered, results similar to those shown in Table 1 were observed (data not shown).

This study is limited in that data were unavailable on several factors that are known to influence a couple's decision to discontinue treatment, such as financial situation, health insurance details, and physician recommendations. Thus we were unable to include these variables in the analysis either as possible predictors or as confounding variables.

In summary, the percentage of women who discontinued IVF treatment after cycle 2 failure was higher than the

TABLE 1

Likelihood of IVF treatment discontinuation by women's characteristics and cycle outcome.

	Discontinuation after cycle 1		Discontinuation after cycle 2	
Predictor	**AOR (95% CI)[a]**	***P* value[b]**	**AOR (95% CI)[a]**	***P* value[b]**
Cycle failure point				
No oocyte retrieval	1.13 (0.77–1.66)	.54	0.65 (0.40–1.05)	.08
Failed fertilization	1.09 (0.72–1.67)	.68	1.29 (0.78–2.13)	.33
Failed implantation	1.00 (reference)		1.00 (reference)	
Chemical pregnancy only	1.51 (1.04–2.17)	.03	1.09 (0.67–1.76)	.74
Clinical pregnancy loss	1.88 (1.22–2.90)	<.01	0.95 (0.52–1.72)	.86
Woman's age at cycle start				
20–34 years	1.00 (reference)		1.00 (reference)	
35–39 years	0.85 (0.65–1.12)	.25	1.36 (0.98–1.89)	.07
40–49 years	1.12 (0.82–1.52)	.49	1.46 (1.01–2.11)	.05
Parity				
No	1.00 (reference)		1.00 (reference)	
Yes	1.58 (1.18–2.10)	<.01	1.66 (1.16–2.37)	<.01

[a] Adjusted odds ratio (95% confidence interval) based on multivariate logistic regression including all variables shown, as well as controlling for study phase and study site. Cohort consisted of 2,245 women commencing cycle 1.
[b] Wald two-sided *P* value.

Pearson. IVF censoring. Fertil Steril 2009.

percentage of women who discontinued after cycle 1 failure (35% and 24%, respectively). Parous women were more likely to discontinue treatment after both cycle 1 and cycle 2, and older women were more likely than younger women to stop treatment after the second cycle. We additionally observed that women who experienced only a chemical pregnancy or a pregnancy loss on the first IVF cycle were more likely to discontinue treatment than those who had an earlier failure point. However, this phenomenon was not observed at the second cycle. Unfortunately, we did not have data on post-IVF cycle spontaneous pregnancy, which could serve as a partial explanation for the higher discontinuation rate of the women experiencing later failure points. That is, women who conceive during their first IVF cycle but experience a pregnancy loss may be more likely to become pregnant "on their own" and therefore not return for a second IVF cycle. Olivius et al. (4) reported that spontaneous pregnancy was the reason for treatment cessation in 19% of cases for which the reason could be ascertained.

Perhaps most interesting, given the observed relationship between treatment discontinuation and postconception cycle failure, is that in the present study, 34% of the women who had at least a chemical pregnancy on cycle 1 had a live birth on cycle 2, compared with only 21% of the women who did not become pregnant in cycle 1. Consistent with our results, Bates and Ginsburg (10) found that women who attained at least a chemical pregnancy on an IVF cycle were more likely to have a live birth on subsequent attempts. Further study, incorporating both the details of previous IVF outcomes and long-term follow up, would be of great interest.

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