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Fertility Treatments and Outcomes among Couples Seeking Fertility Care: Data from a Prospective Fertility Cohort in the United States

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Abstract

Objective—To determine the relationship between number of fertility treatment cycles and pregnancy rates.

Design—Prospective cohort study

Setting—Eight community and academic infertility practices

Patients—408 couples presenting for an infertility evaluation

Interventions—Face-to-face and telephone interviews and questionnaires

Main Outcome Measures—Incidence of pregnancy

Materials and Methods—Cox regression analysis compared the efficacy of cycle-based fertility treatments to no cycle-based fertility treatment after multivariable adjustment

Results—Couples using 1–2 medications-only cycles had a significantly higher pregnancy rate (HR 4.7 [95% CI 1.3–16.6]); a benefit that did not persist after 3+ cycles (HR 0.6 [0.1–3.2]). Couples using IUI for one (HR 2.9 [1.4–5.8]), two (HR 2.0 [0.9–4.5]), and three cycles (HR 4.5 [1.8–10.9]) were more likely to achieve a pregnancy. No additional benefit was seen for couples using 4+ IUI cycles (HR 1.0 [0.4–2.6]). IVF was associated with significant benefit for couples using one (HR 2.8 [1.5–5.2]) and two cycles (HR 2.2 [1.2–4.1]). Couples using 3+ IVF cycles had a non-statistically significant higher likelihood of pregnancy (HR 1.3 [0.7–2.4]).

Conclusions—Cycle-based fertility treatments may offer a point of diminishing returns for infertile couples: two cycles of medications only, three cycles of IUI, and two cycles of IVF.

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Keywords

Diminishing returns; infertility treatment; prospective cohort; decreasing efficacy; ART

Introduction

Infertility affects 7–17% of all couples seeking to have children in the United States (1–5). Regardless of the etiology, infertility treatment has become increasingly "cycle-based" whereby ovarian stimulation by oral and/or injectable drugs is combined with a sperm-delivery technique, usually intrauterine insemination (IUI), in-vitro fertilization (IVF), or intracytoplasmic sperm injection (ICSI). Several studies have demonstrated a benefit of IUI compared to ovarian stimulation alone (6–8), and of IVF compared to IUI (9–11).

There has been significant debate concerning the number of treatment cycles couples should pursue (12,13). Reindollar demonstrated that proceeding to IVF after three IUI cycles resulted in a faster time to pregnancy than using up to six IUI cycles before IVF (13). Data from SART demonstrated that cumulative ART pregnancy rates plateau after 3–4 cycles (14). However, the per-cycle pregnancy rate declined slowly from a maximum of 30% for couples using one cycle to ~20% for couples using 6+ cycles. These data were not adjusted for the many factors known to affect fertility success, nor were they compared to couples not using ART.

Despite these observations, no prospective study has compared these cycle-based fertility treatment modalities in the same study population. Further, few studies have addressed whether the pregnancy rates of the most commonly utilized cycle-based treatments diminish with increasing duration of treatment in a broad population of fertility patients (15). The present study reports results from an 18-month prospective observational study of couples pursuing the full range of cycle-based fertility treatments. The aims of the present study were to describe the use, duration, and success of cycle-based treatments over this period while adjusting for infertility risk factors such as maternal age (16), infertility duration and diagnosis (17–19), and parity (20–22). Such information could be useful in counseling infertile patients as to when they should abandon less intensive treatment for more intensive and potentially more costly therapy.

Methods

Cohort Description

Couples were recruited from eight reproductive endocrinology clinics after the female partner presented for infertility treatment. Study inclusion criteria were: currently trying to get pregnant with a male partner, English-speaking, no prior treatment with IVF, no prior sterilization or hysterectomy, not seeking treatment for recurrent miscarriage, and living in proximity to one of the eight centers. Participants completed baseline questionnaires and face-to-face interviews with highly trained female interviewers and completed three follow-up telephone interviews. Of 809 women who met inclusion criteria, 436 (54%) agreed to participate, and 96% (n=420), 93% (n=405), and 89% (n=390) completed the first (4-month), second (10-month), and third (18-month) follow-up interview, respectively. 408 couples (94%) were followed until pregnancy or study end. The institutional Committee on Human Research approved this protocol and all subjects provided written consent.

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Primary Outcome

Pregnancies were ascertained during semi-structured follow-up interviews. Follow-up time was calculated as time between enrollment date and the interview date at which pregnancy was reported. Couples were censored after the interview in which they reported a pregnancy or at 18 months of observation. Pregnancy status at the time of interview or at the conclusion of the study was the "event" for the survival analysis. The unit of time for each of these "events" was the time between study enrollment and interview date or conclusion of the study.

Predictors

Demographic characteristics—Female and male age, parity and gravidity were determined from baseline questionnaires and the medical record

Fertility characteristics—Duration of infertility was calculated as time between the date the couple began trying to achieve pregnancy and the date of the first interview. Etiology of infertility was obtained through medical record abstraction at the end of the 18-month observation period. Male factor diagnoses were combined into one group ("male factor") while female infertility diagnoses were categorized as tubal (e.g. damaged, blocked, removed Fallopian tubes; ectopic pregnancy; tubal adhesions), uterine (e.g. intrauterine adhesions, fibroids), ovarian (e.g. diminished ovarian reserve, "advanced maternal age," elevated FSH, premature ovarian failure), or ovulatory (e.g. amenorrhea, luteal phase defect, polycystic ovarian disease). A diagnosis of male factor infertility was determined from a review of the medical record. Diagnoses were further classified into 4 groups: no identified infertility etiology, male factor only, female factor only, or both male and female factors. No identified infertility etiology was chosen as the analytic reference group to maximize the clinical applicability and interpretability of these results.

Infertility treatment(s) used was (were) determined through medical record review and interviews in which participants were asked about treatments used since the previous interview. Couples were classified into one of four treatment groups based on the highest treatment intensity used during the study period: No cycle-based treatment (NO_TX), ovulation induction without IUI (MEDS), IUI with or without ovulation induction (IUI), and IVF with or without preceding IUI (IVF). Couples using donor egg were excluded from the IVF group. The number of treatment cycles used for each cycle-based treatment pathway was tabulated.

Data Analysis

Kaplan-Meier analysis estimated the cumulative probability of ongoing pregnancy after study enrollment (23). The log-rank test assessed bivariate differences between subject characteristics and the likelihood of pregnancy. Pair-wise and overall p-values are reported for each covariate. Multivariable Cox proportional hazards regression analysis estimated the effect of treatment type and number of treatment cycles on the probability of pregnancy after adjustment for age, parity, and infertility duration and diagnosis. We report Hazard Ratios (HR) with 95% confidence intervals to estimate the association between these subject characteristics and the monthly probability of pregnancy. Proportional hazards assumptions were assessed by careful visual inspection of log/antilog survival curves to assess for marked divergences, convergences, or multiple crossings of survival curves. We also applied the Schoenfeld test to all variables in the regression models. All variables listed above met the proportional hazards assumptions.

Initial multivariable Cox proportional hazards models were developed with predictor variables selected *a priori*. For the three models comparing the number of MEDS, IUI, or

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IVF cycles to NO_TX, covariates included: male and female age, male factor infertility, female diagnosis, female parity, fertility treatments prior to study enrollment, and infertility duration. The model evaluating the effect of IUI also adjusted for the number of medication-only cycles. The multivariable model characterizing IVF adjusted for the number of medication-only and IUI cycles. Statistical significance was set at $p<0.05$; all tests were 2-sided. STATA 10 (Statacorp, College Station, TX, USA) was used for all analysis.

Results

Among 408 participants, mean female and male ages were 35.6 (SD 4.7) and 36.9 (SD 5.5), respectively. Female factor infertility was found most commonly (58%, Table 1). Mean infertility duration was 2.1 years (SD 1.7). Fertility treatment prior to enrollment in the study was relatively common and included clomiphene (65%), gonadatropins (25%), and IUI (36%). Female age ($p = 0.08$), male age ($p = 0.38$), having prior children ($p = 0.10$), using oral medications before study entry ($p=0.06$), duration of infertility ($p = 0.39$), and uterine factor infertility ($p = 0.28$) were not significantly associated with treatments used during the study. However, couples who used injection medications ($p = 0.01$) or IUI ($p < 0.001$) prior to study entry, overall couple infertility etiology ($p = 0.002$), tubal factor infertility ($p = 0.02$), ovarian factor infertility ($p = 0.03$), and ovulatory dysfunction ($p < .001$) were significantly associated with subsequent treatment type. During the study period, treatments used were IVF (53%), IUI (22%), and MEDS (4%); 21% used NO_TX. Most couples used three or fewer treatment cycles (47%); however, a substantial minority used 4+ cycles (32%). The cumulative pregnancy rate was lowest for couples using NO_TX (28%) compared to 50–70% for IUI, and 35–60% for IVF (Table 2).

Women > age 40 were 71% less likely to achieve pregnancy (HR 0.29 [95% CI 0.18–0.45]) compared to women < age 35 (Table 3). Couples with men aged 35–39 and those > age 40 were 30% (HR 0.70, [0.51–0.97]) and 44% (HR 0.56 [0.39–0.81]), respectively, less likely to achieve pregnancy relative to men < age 35. Relative to couples with no known infertility factors, couples with isolated female factor infertility were 55% less likely to achieve pregnancy (HR 0.45 [0.3–0.8]). Those with both male and female factors were 64% less likely to become pregnant (HR 0.36 [0.20–0.64]). Isolated male factor infertility was associated with a non-statistically significant 33% reduction in the probability of achieving a pregnancy.

In unadjusted analyses, cycle-based treatment was associated with a 2.3-fold increase in monthly pregnancy rates (HR 2.3 [1.5–3.4], Table 3) compared to NO_TX. Using MEDS was more effective than NO_TX for 1–2 cycles (HR 5.39 [2.4–12.2]), but not for 3+ cycles (HR 0.9 [0.2–3.7]). IUI was more effective than NO_TX for one (HR 3.1 [1.8–5.4]), two (HR 2.9 [1.5–5.6]), and three (HR 3.1 [1.5–6.3]) cycles; however, no statistical improvement in pregnancy rate occurred after 4+ cycles. IVF was significantly more effective than NO_TX for one (HR 2.5 [1.5–4.0]), two (HR 2.5 [1.5–4.1]), and 3+ cycles (HR 1.5 [0.9–2.6]); however, this difference was not statistically significance for couples using3+ cycles.

After adjustment for infertility diagnosis, male and female age, parity, infertility duration, and fertility treatment used before study enrollment, the MEDS group was associated with a significant increase in the monthly incidence of pregnancy after 1–2 cycles (HR 4.7 [1.3–16.6]; Table 4), but not for 3+ cycles (HR 0.6 [0.1–3.2]). Of the covariates examined, only female age >40 was independently associated with lower success rates (HR 0.06 [0.01–0.4]).

A similar pattern was seen for IUI cycles after multivariable adjustment for infertility diagnosis, male and female age, parity, infertility duration, fertility treatment used before

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study enrollment, and number of failed medication cycles during the study. IUI was better than NO_TX for one (HR 2.85 [1.4–5.8]), two (HR 2.0 [0.9–4.5]), and three (HR 4.5 [1.8–10.9]) cycles; however, this difference was not statistically significance for couples using two cycles. Couples using 4+ cycles were no more likely than the NO_TX group to achieve pregnancy (HR 1.0 [0.4–2.6]). Female age >40 (HR 0.11 [0.03–0.3] tubal diagnosis (HR 0.3 [0.09–0.9]), and male factor infertility (HR 0.57 [0.3–1.0]) were independently associated with lower success rates.

After multivariable adjustment, IVF was more effective than NO_TX for couples using one (HR 2.8 [1.5–5.2]) and two cycles (HR 2.2 [1.2–4.1]). While IVF was associated with a 25% increase in the monthly pregnancy rate for couples using 3+ cycles (HR 1.25 [0.7–2.4]), this increase was not statistically significant. Female age >40 (HR 0.35 [0.2–0.8]) was independently associated with a 65% reduction in the likelihood of achieving a pregnancy relative to couples with women under 35. When the female partner had one or more prior children, her likelihood of achieving a pregnancy also increased significantly (HR 1.6 [1.0–2.5]).

Discussion

To the best of our knowledge, no study in the United States has prospectively determined the incidence of pregnancy among a population of couples seeking infertility consultation who utilized a wide range of fertility options, nor has any prospective study determined the optimal length of time to pursue particular treatment options before considering higher intensity treatment. Data from this study demonstrated a decreasing efficacy of cycle-based infertility treatment over the course of 18 months of follow-up.

Compared to no treatment, the first several cycles of medications, IUI, or IVF increased pregnancy rates. However, there was a point of diminishing returns where additional cycles did not significantly alter pregnancy rates. After adjustment for common infertility risk factors, couples using medications only for one or two cycles had a five-fold higher average monthly pregnancy rate than who did not use cycle-based treatment. This benefit did not persist for couples using three or more such cycles. Couples using IUI had higher pregnancy rates through three cycles but not for 4+ cycles. IVF was associated with more than a doubling in the probability of achieving pregnancy for couples using one or two cycles. Using 3+ cycles of IVF was associated with a non-statistically significant 25% increase in pregnancy rates, supporting a recent U.S. retrospective cohort study that found that pregnancy rates decline with increasing treatment time (12).

The decline in treatment efficacy with repeated cycles was most pronounced for couples using medications or IUI alone. This rapid decline in treatment efficacy over time may reflect more severe underlying fertility problems in couples not achieving pregnancy within the first few cycles of treatment. For IVF, a persistent benefit cannot be ruled out from our data. Estimates from the SART Writing Group (14) demonstrate a cumulative IVF pregnancy rate of ~50% after 3 cycles, increasing to only 56% after 9+ cycles, with a slow decline in per-cycle IVF pregnancy rates from 30% for couples using one cycle to 20% for couples using 9+ cycles.

The choice to forego cycle-based treatment appears to have merits for a short time. An earlier cohort study of 873 untreated infertile couples demonstrated an annual pregnancy rate of ~14% (24), slightly lower than the 22% observed in our no-cycle-based treatment population. The higher rate in our study could be explained by the utilization of non-cycle based treatments, differences in the study population, or statistical variation. A recent large prospective study of couples in the Netherlands demonstrated that 9% of infertile women on

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an IVF/ICSI waiting list achieved a treatment-independent pregnancy within one year of observation (25). These studies did not characterize the rate at which couples achieved pregnancy. We found that the pregnancy rate was similar between treated and untreated patients for the first 4–6 months, after which time the pregnancy rate began to flatten for the no-cycle-based treatment group and increase for the cycle-based treatment patients. While using no cycle-based treatment may be a reasonable initial approach, particularly for women <age 35, if the couple's goal continues to be achieving a pregnancy, they may be better served by considering use of cycle-based treatments after six months.

Few prospective cohorts have evaluated the effect of risk factors among a general fertility population. Increasing female age was consistently associated with lower pregnancy rates, while male age became statistically insignificant after adjustment for female age. This likely represents the observation that men and women, on average, marry at similar ages and that female age represents the stronger influence on fertility. Fertility diagnosis was also an important predictor of pregnancy. Couples with no known infertility factors were more likely to achieve a pregnancy, while female factor infertility, particularly ovarian dysfunction (e.g., diminished ovarian reserve), was a significant factor in lower pregnancy success. Tubal infertility was not associated with lower pregnancy success, probably because these couples were more likely to undergo IVF.

We acknowledge that some couples pursued multiple cycles of cycle-based therapy early in observation while others pursued treatment later, leading to variations in time to pregnancy not due to subject characteristics or treatments.. Despite this limitation, a real time cumulative pregnancy rate was calculated as suggested by Daya (23), who advocated this approach as the optimal technique. It was not possible to calculate per-cycle success rates for treatment given the fact of follow-up at 4, 10, and 18 months. Finally, because the sample size for each treatment group was relatively small, extensive inference was not possible for many of these subgroups. We suspect that future, larger prospective studies will demonstrate a similar pattern of decreasing treatment effectiveness but perhaps with different cutoff points for treatment efficacy.

Nevertheless, this study is the largest prospective study performed in the United States comparing outcomes of cycle-based fertility treatments to no-cycle-based treatments. Losses to follow-up were very small, suggesting that informative censoring (e.g. drop-out due to poor prognostic findings or psychological distress) did not threaten the internal validity of this study. Finally, using couple-based (rather than cycle-based) data provides information that may be more relevant to counseling patients considering different treatment pathways.

Our data suggest that while cycle-based fertility treatments offer clinically significant increases in the pregnancy rate; this benefit does not persist indefinitely. Couples not achieving a pregnancy on medications alone after two cycles or IUI after three cycles may be best counseled to pursue a higher level of infertility treatment, consistent with recent work by Reindollar (13). Those failing IVF after two cycles may want to consider other treatment strategies such as donor sperm, donor egg, or further modifications in the IVF or ICSI protocol as additional cycles appear less likely to increase reproductive success as much as earlier cycles.

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Table 1

Age and Fertility Characteristics of Cohort (N=408)

		N	%
Female age	<35	162	39.8
	35–39	156	38.3
	≥40	89	21.9
Male Age	<35	126	30.9
	35–39	129	31.6
	≥40	101	24.8
	Unknown	52	12.8
Prior offspring		97	23.9
Prior pregnancy	0	193	49.6
	1	92	23.7
	2	64	16.5
	3+	40	10.3
Prior fertility treatment	Oral medications	251	65.4
	Injectable medications	94	24.5
	IUI	139	36.2
Duration of infertility	< 1 year	69	16.9
	1–2 years	158	38.7
	≥ 2 years	152	37.3
	Unknown	29	7.1
Couple fertility diagnosis	Male and female factors	123	30.2
	Female factor only	238	58.3
	Male factor only	29	7.1
	No known infertility factors	18	4.4
Female diagnosis	Tubal	57	14.0
	Uterine	48	11.8
	Ovarian	155	38.0
	Ovulatory	109	26.7
Donor Egg		24	5.9
Number of cycles	0	86	21.1
	1	68	16.7
	2	65	15.9
	3	57	14.0
	4	38	9.3
	5	28	6.9
	6	27	6.6
	7+	39	9.6
	No cycle-based treatment	86	21.1
Highest intensity of fertility treatment	Medications only	15	3.7
	Intrauterine insemination only	91	22.3

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	N	%
In vitro fertilization	216	52.9

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Table 2

Cumulative Pregnancy Rate at Eighteen Months by Treatment Type and by Couples Using a Given Number of Cycles

Number of Cycles	N	Cumulative Pregnancy Rate*	95% CI	
No Cycle-Based Treatment	86	0.28	0.20	0.39
Medications Only				
1–2 cycles	9	0.85	0.54	0.99
3+ cycles	6	0.29	0.08	0.74
Intrauterine Insemination				
1 cycle	33	0.71	0.55	0.85
2 cycles	23	0.57	0.38	0.77
3 cycles	15	0.71	0.48	0.90
4+ cycles	20	0.50	0.28	0.76
In-Vitro Fertilization				
1 cycle	83	0.59	0.48	0.71
2 cycles	57	0.57	0.44	0.70
3+ cycles	52	0.35	0.23	0.50

*Cumulative pregnancy rates for population of couples utilizing each number of cycles. Couples using donor egg were excluded from IVF cycles.

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Table 3

Unadjusted Relationship between Age, Fertility Characteristics, Treatments, and the Monthly Likelihood of Achieving a Pregnancy

		N	HR	95% CI		P-Value	Overall P-Value
Female age	<35	162	1.00	ref		ref	
	35–39	156	0.78	0.58	1.03	0.08	
	≥ 40	89	0.29	0.18	0.45	<0.001	<0.001
Male age	<35	126	1.00	ref		ref	
	35–39	129	0.70	0.51	0.97	0.03	
	≥40	101	0.56	0.39	0.81	<0.001	
	Unknown	52	0.53	0.33	0.84	0.01	0.004
Prior children	No	309	1.00	ref		ref	
	Yes	97	1.10	0.81	1.50	0.53	0.53
Prior pregnancy	0	193	1.00	ref		ref	
	1	92	1.15	.82	1.62	.40	
	2	64	1.22	.83	1.81	.30	
	3+	40	.81	.49	1.32	.39	.41
Prior fertility treatment	Oral medications	251	1.05	0.79	1.40	0.74	0.74
	Injectable medications	94	1.26	0.92	1.71	0.15	0.15
	IUI	139	1.04	0.79	1.40	0.74	0.74
Duration of infertility	< 1 year	69	1.00	ref		ref	
	1–2 years	158	1.30	0.88	1.92	0.18	
	≥ 2 years	152	0.89	0.59	1.33	0.56	
	Unknown	29	0.69	0.35	1.37	0.29	0.03
Couple fertility diagnosis	No known infertility factors	18	1.00	ref		ref	
	Male factor only	29	0.67	0.34	1.34	0.26	
	Female factor only	238	0.45	0.26	0.78	0.01	
	Male and female factors	123	0.36	0.20	0.64	<0.001	0.002
Female diagnosis	Tubal	57	0.94	0.64	1.40	0.77	0.77
	Uterine	48	0.77	0.49	1.21	0.26	0.26
	Ovarian	155	0.60	0.45	0.81	<0.001	<0.001
	Ovulatory	109	1.29	0.96	1.73	0.09	0.09
Any cycle-based treatment	No	86	1.00	ref		ref	

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		N	HR	95% CI		P-Value	Overall P-Value
	Yes	322	2.28	1.51	3.43	<0.001	<0.001
Medications only	No cycle based treatment	86	1.00	ref		ref	
	1–2 cycles	9	5.39	2.39	12.16	<0.001	
	3+ cycles	6	0.87	0.20	3.67	0.85	<0.001
Intrauterine insemination only	No cycle based treatment	86	1.00	ref		ref	
	1 cycle	33	3.14	1.81	5.44	<0.001	
	2 cycles	23	2.93	1.52	5.62	<0.001	
	3 cycles	15	3.12	1.53	6.34	<0.001	
	4+ cycles	20	1.63	0.79	3.39	0.19	<0.001
In vitro fertilization only	No cycle based treatment	86	1.00	ref		ref	
	1 cycle	83	2.46	1.52	3.98	<0.001	
	2 cycles	57	2.45	1.47	4.07	0.001	
	3+ cycles	52	1.49	0.85	2.59	0.16	<0.001

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Table 4

Multivariable Relationship between Number of Fertility Treatments and the Monthly Likelihood of Achieving a Pregnancy

Medication Use*		**N**	**HR**	**95% CI**		**P-Value**	**Overall P-Value**
Number of cycles	No cycle based treatment	86	1.00	ref		ref	
	1–2 cycles	9	4.71	1.34	16.64	0.02	
	3+ cycles	6	0.63	0.13	3.18	0.58	0.03
Intrauterine Insemination Use**							
Number of cycles	No cycle based treatment	86	1.00	ref		ref	
	1 cycle	21	2.85	1.40	5.82	0.004	
	2 cycles	23	2.03	0.93	4.47	0.08	
	3 cycles	15	4.47	1.83	10.9	0.001	
	4+ cycles	32	1.04	0.41	2.62	0.94	0.006
In-Vitro Fertilization Use***							
Number of cycles	No cycle based treatment	86	1.00	ref		ref	
	1 cycle	83	2.78	1.48	5.24	0.001	
	2 cycles	57	2.21	1.19	4.11	0.01	
	3+ cycles	52	1.25	0.65	2.41	0.51	0.003

* Adjusted for male and female age, male factor infertility, female diagnosis (i.e. tubal, uterine, ovarian, ovulatory), parity, prior fertility treatments and duration of infertility. Of note, only female age over 40 compared to under 35 (HR 0.06, p=0.005) was independently associated with lower pregnancy success.

** Adjusted for male and female age, male factor infertility, female diagnosis (i.e. tubal, uterine, ovarian, ovulatory), parity, number of failed medication cycles, prior fertility treatments (i.e. prior medication use or intrauterine insemination) before study entry, and duration of infertility. Of note, female age over 40 (HR .11, p = 0.001), tubal factor (HR 0.29, p=0.04), and male factor (HR 0.57, p=0.05) were independently associated with lower success.

*** Adjusted for male and female age, male factor infertility, female diagnosis (i.e. tubal, uterine, ovarian, ovulatory), parity, prior fertility treatments (i.e. prior medication use or intrauterine insemination) before study entry, number of failed medication and IUI cycles during the study, and duration of infertility. Couples using donor egg were excluded from IVF cycles. Of note, female age over 40 (HR 0.35, p=0.01) and having a previous child (HR 1.59, p = 0.04) were independently associated with pregnancy success.