Journal of Andrology, Vol. 33, No. 3, May/June 2012

Donor Sperm Insemination Cycles: Are Two Inseminations Better Than One?

DIANA E. CHAVKIN,* THOMAS A. MOLINARO,* ANDREA H. ROE,* MARY D. SAMMEL,† AND ANUJA DOKRAS*

*From the *Department of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia, Pennsylvania; and the †Department of Biostatistics and Epidemiology Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.*

ABSTRACT: The objective of this study was to determine the clinical pregnancy rate with 2 inseminations compared to a single intrauterine insemination (IUI) in a given cycle using frozen-thawed donor sperm. This was a retrospective study at a university practice; patients were women using donor sperm. We conducted a comparison of single IUI, intracervical insemination (ICI) followed by an IUI on the next day, and double IUI (2 consecutive days); clinical pregnancy rate was the main outcome measure. The cycle-specific and total pregnancy rates were not significantly different between the 3 protocol groups (306 cycles). The average pregnancy rate over 3 cycles was 10.2% for IUI, 15.3% for ICI/IUI, and 13.7% for IUI/IUI (P = .47). After controlling for repeated measures per subject and age, gravidity, and use of Clomid, there was no significant difference between protocols. The ICI/IUI (odds ratio [OR] = 1.70; 95% confidence interval [CI], 0.83–3.51) and IUI/IUI (OR = 1.5; 95% CI, 0.52–4.33) protocols appeared more likely to result in a clinical pregnancy than the single IUI protocol. Current information on the optimal number of inseminations per cycle using donor sperm is limited. Our large study using 3 protocols found an increase in pregnancy rate with the addition of either an ICI or IUI to a single IUI protocol in a natural or Clomid cycle but did not meet statistical significance. Additional prospective studies are needed to better counsel patients using donor sperm.

Key words: Donor sperm, intrauterine inseminations, intracervical inseminations, pregnancy rate, Clomid.

J Androl 2012;33:375–380

Donor sperm insemination is the first line of treatment for couples with an azoospermic male partner, single women, and same-sex female couples. All donor sperm samples are cryopreserved, allowing for appropriate testing of the donors for infectious diseases. Intrauterine insemination (IUI) or intracervical insemination (ICI) of the frozen-thawed samples can then be performed to achieve pregnancy. The ICI procedure is less invasive, typically using unwashed sperm, and costs less compared to the IUI procedure. A meta-analysis of 7 prospective randomized studies comparing single ICI or IUI using frozen-thawed donor sperm showed that IUI had a significantly higher monthly fecundity rate (odds ratio [OR] = 2.4; 95% confidence interval [CI], 1.5–3.8; Goldberg et al, 1999). These studies included both natural cycles and treated (clomiphene or injectable gonadotropins) cycles. More recently, a Cochrane systematic review reported significantly higher cumulative pregnancy rates (OR = 3.37; 95% CI, 1.9–5.96) and live birth (OR = 1.98; 95% CI, 1.02–3.86) after 6 treated cycles of frozen-thawed donor sperm IUI compared to ICI (Besselink et al, 2008).

Accurate timing of the insemination procedure to coincide with ovulation is important when exposure to sperm is limited to only the insemination procedure. To overcome this limitation in a patient using donor sperm, the number of inseminations per cycle can be increased to include a combination of either ICI-IUI or IUI-IUI on consecutive days. Most of the current data for the optimal number of inseminations to be performed in a cycle come from fresh partner insemination cycles rather than donor cycles. In a meta-analysis of 6 randomized studies of couples with unexplained infertility, double inseminations within a cycle did not increase the odds of clinical pregnancy compared to a single insemination when using fresh sperm (Polyzos et al, 2010). In another meta-analysis and systematic review including couples with all causes of infertility, double inseminations of fresh sperm resulted in significantly higher pregnancy rates compared to single insemination (Cantineau et al, 2003). The outcomes of double vs single inseminations in couples using fresh sperm, however, cannot be applied to women using frozen-thawed donor sperm. One reason is the inability to accurately control for the actual number of inseminations per cycle in couples not using donor sperm (usually instructed to have intercourse

Correspondence to: Dr Anuja Dokras, 3701 Market St, Suite 800, Philadelphia, PA 19105 (e-mail: adokras@obgyn.upenn.edu).

Received for publication February 10, 2011; accepted for publication May 23, 2011.

DOI: 10.2164/jandrol.111.013276

in the periovulatory period). Also, fresh donor sperm insemination cycles have a significantly higher success rate compared to frozen-thawed donor sperm insemination cycles ($P < .001$) (Botchan et al, 2001). These differences in success rates may be related to different postthaw characteristics of frozen sperm. The current practice of using only quarantined donor sperm for insemination necessitates further investigation of the benefits of double inseminations.

Therefore, the question still remains: does the addition of a second insemination within the same cycle provide increased number of thawed sperm around the periovulatory period to increase the pregnancy rates? The literature that addresses this specific question in donor sperm frozen-thawed insemination cycles is limited and conflicting. A few studies using either natural cycles or ovarian stimulation showed benefit from double inseminations (Centola et al, 1990; Deary et al, 1997; Matilsky et al, 1998) and 1 study did not show any benefit (Khalifa et al, 1995). Two of these studies, however, compared single vs double ICIs (Centola et al, 1990; Deary et al, 1997). One prospective study using frozen-thawed donor sperm demonstrated a 2-fold probability of conception over 15 cycles in patients who received double IUI (Matilsky et al, 1998). At this time, there is evidence to support use of single IUI rather than single ICI in women using frozen donor sperm (Goldberg et al, 1999; Besselink et al, 2008); however, it remains unclear whether adding a second ICI or IUI insemination in a given cycle will increase the chance of pregnancy.

Determining the most cost-effective strategy for use of donor sperm is necessary to maximize the likelihood of pregnancy while limiting emotional and financial costs. The cost of using donor sperm is infrequently covered by health insurance plans in the United States. Cryopreservation and thaw methods decrease sperm motility and viability, requiring more treatment cycles to achieve comparable success rates to cycles using fresh sperm (Botchan et al, 2001). The primary aim of our study was to determine the clinical pregnancy rate per cycle in 3 frozen-thawed donor sperm insemination protocols, namely single insemination with IUI, 2 inseminations with ICI followed by IUI the next day, and 2 inseminations with IUI on consecutive days.

Materials and Methods

A retrospective cohort study was performed with institutional review board approval. Women who had undergone frozen-thawed donor sperm inseminations from 2000 to 2008 at Penn Fertility Care, University of Pennsylvania, were identified through the andrology database. Medical records were reviewed and subjects were included if they had undergone donor sperm inseminations without exposure to fresh sperm from another source (single women, same-sex female partners, and azoospermic males) and had complete records. Women had a preliminary workup including endocrine hormone evaluation and tubal patency testing prior to starting inseminations. Both stimulated (clomiphene citrate) and nonstimulated (natural) cycles were included. The first line of treatment was generally nonstimulated cycles in younger subjects and stimulated cycles in older subjects. Single inseminations were performed on the day after the luteinizing hormone (LH) surge was first detected, whereas double inseminations included an insemination on the day the LH surge was detected and on the following day. In the few instances when patients were unable to detect an LH surge, ultrasound monitoring was performed. The thawed sperm were inseminated in the cervix using a Soft Pass insemination catheter (Cook, Bloomington, Indiana) and in the uterus using an Insemi-Cath catheter (Cook). Subjects were asked to remain supine for 10–15 minutes after the insemination procedure.

Abstracted data were limited to each woman's first 3 insemination cycles because previous studies have indicated that the chance of achieving a pregnancy during the first 3 cycles is similar to and higher than in subsequent cycles (Aboulghar et al, 2001). The primary outcome of interest was clinical pregnancy, defined as an intrauterine gestational sac seen on ultrasound examination. Patient demographics, cause of infertility, and treatment cycle parameters were abstracted from medical records and entered into an electronic database. During a patient's initial evaluation, the treatment plan for 1 or 2 inseminations was presented to all patients, and the choice of protocol was based on treatment costs, time commitment for repeated inseminations in 1 cycle, and patient preference. Patients were counseled that there were no clear data to suggest a difference in success rates between these protocols when using frozen sperm.

Treatment cycle parameters included cycle number and protocol type used in that specific cycle. The protocol types were 1) 1 IUI, 2) ICI followed by IUI, and 3) IUI followed by another IUI in a given cycle. The specific protocol selected for a particular cycle was the exposure of interest, and each protocol was compared with the other 2 protocols. In addition, the analysis included the cycle number, that is, whether the protocol was performed in a given patient's first, second, or third cycle attempt. Because each woman could have undergone a different combination of protocols over their first 3 cycles, we compared the specific treatment protocols (ie, all IUI cycles were compared with all ICI/IUI cycles and with all IUI/IUI cycles). Given this design, it is not possible to compute cumulative pregnancy rates per woman per protocol because some subjects switched from one treatment to another in subsequent cycles. Therefore, we utilized an analytic method that allowed us to evaluate cycle-specific success for each treatment, which is then averaged over the 3 observed cycles.

We did not exclude patients based on the ovarian stimulation protocol or presence of an infertility diagnosis to allow wider applicability of our results. We used regression analysis to control for covariates such as use of Clomid and presence of infertility diagnosis in addition to controlling for multiple cycles per subject.

Table 1. *Demographics and treatment parameters of patients included in the 3 insemination protocols*[a]

	IUI	ICI/IUI	IUI/IUI
No. of cycles	137	118	51
No. of cycles, mean ± SD	2.6 ± 0.7	2.6 ± 0.7	2.6 ± 0.7
Age, y, mean ± SD	36 ± 4.7	35.8 ± 4.1	36.6 ± 4.3
Infertility diagnosis (PCOS, endometriosis, tubal factor, or DOR), No. (%)	51 (37)	27 (23)[b]	16 (31.4)
Prior gravidity, No. (%)	22 (15)	20 (16)	15 (29)
Sperm motility, %, mean ± SD	41.8 ± 11	44.3 ± 7.4[b]	44.0 ± 11.9
Sperm count, 10^6/mL, mean ± SD	54.7 ± 24.5	59.6 ± 18[b]	60.7 ± 24.9
Ovarian stimulation (Clomid), No. (%)	77 (57)	53 (46)	22 (45)

Abbreviations: DOR, diminished ovarian reserve; ICI, intracervical insemination; IUI, intrauterine insemination; PCOS, polycystic ovary syndrome.

[a] Comparisons made using Pearson Chi-square or Wilcoxon rank-sum as appropriate.

[b] $P < .05$ compared to IUI group.

Statistical analysis was performed with STATA v. 10 (College Station, Texas). The Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables were used to compare baseline demographics between the 3 protocols. Pairwise comparisons between specific protocols were performed using Mann-Whitney and χ^2 tests when indicated. Cycle-specific pregnancy rates between the protocols were compared using the χ^2 test of proportions, given that data from each cycle are independent. We also fit a generalized linear regression model using the generalized estimating equation (GEE) framework (Zeger and Liang, 1986) to evaluate covariates in the multivariable model, allowing us to simultaneously evaluate multiple cycles per subject yet also to estimate and adjust the statistical tests of significance to control for the correlation in responses induced by multiple cycles contributed from each subject. This extension of multivariable logistic regression also allows for the control of confounding covariates of interest such as use of Clomid and presence of infertility diagnosis, in addition to controlling for multiple cycles per subject. Our prestudy power calculation indicated that we needed 118 cycles in each protocol group to find a 2-fold difference between groups with 80% statistical power. A doubling of the pregnancy rate was assumed clinically important, given that the cost of 2 IUIs within a cycle is comparable to that of performing a single IUI in 2 consecutive cycles.

Results

We identified a total of 333 donor insemination cycles (limited to the first 3 cycles) in 156 women. Twenty-seven cycles from 9 women were excluded, as they had undergone a single ICI or had been treated with injectable gonadotropins. The final dataset included 306 cycles from 145 patients: 137 cycles with single IUI, 118 cycles with double insemination consisting of ICI on one day followed by an IUI on the next day (ICI/IUI), and 51 cycles with double insemination consisting of IUI on one day followed by an IUI on the next day (IUI/IUI). The 145 women included in this study could have undergone the same or a different protocol in subsequent cycle attempts. The majority of women (86/145) experienced only 1 protocol type (35 women underwent IUI, 37 had ICI/IUI, and 14 had IUI/IUI). The remaining 59 women underwent some combination of the 3 different protocols. There were no significant differences in mean age or mean number of cycles between protocol groups (Table 1). However, infertility diagnosis and sperm parameters were significantly different in the ICI/IUI vs the single IUI protocols.

The unadjusted cycle-specific and total pregnancy rates were not significantly different between the treatment protocols (Table 2). When the analysis was limited to the same cycle number, that is, first, second, or third, there were no significant differences in pregnancy rates between protocols. The total success rates after 3 cycles were 10.2% for single IUI, 15.3% for ICI/IUI, and 13.7% for IUI/IUI ($P = .47$). In addition, within a particular treatment arm, there were no significant differences in pregnancy rates regardless of

Table 2. *Per-cycle and total pregnancy rates using frozen-thawed donor sperm for inseminations.* P *values compared rates between all 3 groups*[a]

	IUI	ICI/IUI	IUI/IUI	*P* Value
No. of cycles	137	118	51	
Cycle 1, No. (%)	8/58 (13.8)	11/50 (22)	3/23 (13.0)	.455
Cycle 2, No. (%)	4/47 (8.5)	5/39 (12.8)	3/9 (33.3)	.121
Cycle 3, No. (%)	2/32 (6.3)	2/29 (6.9)	1/19 (5.3)	.974
Cycle totals, No. (%)	14/137 (10.2)	18/118 (15.3)	7/51 (13.7)	.473

Abbreviations: ICI, intracervical insemination; IUI, intrauterine insemination.

[a] Comparisons made using Pearson Chi-square.

Table 3. *Estimated cumulative pregnancy rates by protocol (utilizing cycle total pregnancy rate from Table 2)*

Cycle No.	IUI	ICI/IUI	IUI/IUI
1, % (No.)	10.2 (14/137)	15.3 (18/118)	13.7 (7/51)
2, %	19.0	28.3	25.5
3, %	27.2	39.6	35.9
4, %	34.7		

Abbreviations: ICI, intracervical insemination; IUI, intrauterine insemination.

whether it was the first, second, or third attempt. The unusually high success rate in the double IUI protocol in cycle 2 (33.3%) is likely due to the very small number of subjects (n = 9) in this protocol group for this cycle.

Given that subjects did not have the same treatment in each cycle, we have also represented our observed data as a standard analysis, that is, we calculated the estimated cumulative pregnancy rates as if each woman had stayed in the same treatment protocol for all her cycles (Table 3). These calculations used the total cycle pregnancy rate from Table 2 as our estimated probability of success for a given protocol, and cumulative success rates were then estimated considering events were independent. This estimation allowed us to compare the 3 protocols over different numbers of cycles. The success rate for the first cycle of 2 IUIs would have been 13.7%, whereas the cumulative success rate for 2 cycles using a single IUI is estimated to be 19% (Table 3). Two successive cycles with the 2-IUI protocol would have resulted in a cumulative success rate of 25.5%, whereas we would anticipate that if a subject had 4 cycles with a single IUI in each then the cumulative success rate would be 34.7%.

The ORs and 95% CIs were determined with the use of logistic regression utilizing the GEE in order to control for potential covariate differences between protocol groups and account for potential correlation in repeated cycles by individual women (Table 4). The GEE is a well-validated method that allows us to evaluate outcomes by making protocol type (treatment group) our independent variable and pregnancy rate (outcome) our dependent variable. Therefore, when analysis is limited to the first 3 cycle attempts, each cycle represents its own independent event that is not statistically dependent upon the outcome of the previous or subsequent cycles. When controlling for repeated cycles per subject, ICI/IUI (OR = 1.54, 95% CI 0.77–3.07) and IUI/IUI (OR = 1.36; 95% CI, 0.52–3.56) protocols both appeared more likely to result in a pregnancy compared to the single IUI protocol. The ICI/IUI protocol also appeared to have a higher pregnancy rate than the IUI/IUI protocol (OR = 1.13; 95% CI, 0.46–2.74). We then performed a multivariable logistic regression analysis, and in our most parsimonious model, when controlling for prior gravidity, use of medication for ovulation induction, and age, all pairwise comparisons failed to meet statistical significance (Table 4). Presence of infertility diagnosis, sperm count, and motility were not significant or confounders and hence were not included in the final model. Although the ICI/IUI (OR = 1.70; 95% CI, 0.83–3.51) and IUI/IUI (OR = 1.5; 95% CI, 0.52–4.33) protocols appeared more likely to result in a clinical pregnancy than the single IUI protocol, this was not statistically significant. In addition, the difference between the ICI/IUI and IUI/IUI protocols was not significantly different (OR = 1.13; 95% CI, 0.43–2.96). In addition, ovarian stimulation with Clomid did not significantly improve the overall success of donor insemination cycles (adjusted OR = 1.02; 95% CI, 0.49–2.10; not shown in table).

Discussion

The primary aim of our study was to determine whether an additional insemination (intracervical or intrauterine) in a frozen-thawed donor sperm insemination cycle would increase the likelihood of pregnancy. We compared 2 protocols (ICI/IUI and IUI/IUI) to a single IUI, as the latter is the standard of care in fresh sperm insemination cycles. We did not find a statistically significant difference between the double inseminations compared to the single-insemination protocol group; however, both double-insemination protocols had higher total pregnancy rates. Moreover, the additional cost of the double insemination is not supported by our data. Larger prospective studies will be needed to address the precise benefit of adding a second insemination.

As mentioned in the introductory section of this article, there is very limited information in the literature

Table 4. *OR and 95% CI for clinical pregnancy rate using logistic regression utilizing GEE*

Controlled For	OR (95% CI)		
	ICI/IUI vs IUI	IUI/IUI vs IUI	ICI/IUI vs IUI/IUI
Repeated measures per subject	1.54 (0.77–3.07)	1.36 (0.52–3.56)	1.13 (0.46–2.74)
Prior gravidity, use of Clomid, age	1.70 (0.83–3.51)	1.50 (0.52–4.33)	1.13 (0.43–2.96)

Abbreviations: CI, confidence interval; GEE, generalized estimating equation; ICI, intracervical insemination; IUI, intrauterine insemination; OR, odds ratio.

Table 5. *Estimated costs for 3 donor insemination protocols*

	IUI	ICI/IUI	IUI/IUI
Sperm sample, $	440	780	880
Procedure cost, $	295	560	590
Laboratory processing, $	150	150	150
Shipping, $	110	110	110
Total, $	995	1600	1730
Clinic visit, d	1	2	2

Abbreviations: ICI, intracervical insemination; IUI, intrauterine insemination.

regarding the number of inseminations when using frozen-thawed sperm. One study compared single vs double IUI in stimulated cycles (Matilsky et al, 1998). Although the pregnancy rate was higher in the double-insemination group, the per-cycle pregnancy rate in the single-IUI group reported in that study (5%) was much lower than our results (10.2%) and may have accounted for the significant difference between groups. The second study did not find an increase in pregnancy rates with the addition of the second IUI (Khalifa et al, 1995). Our study had several advantages. We included a third protocol, namely ICI/IUI, which provides the patients the option of a less expensive treatment compared to IUI/IUI. We restricted our study to the first 3 cycles in each treatment group, as it has been reported that couples using IUI are more likely to achieve pregnancy within the first 3 cycles (Smith et al, 2010). We also included women who switched treatment protocols from one cycle to the next, which reflects the reality of clinical practice in this patient group and allows for increased study power. The methodological strengths of our study are the inclusion of unselected patients and use of a well-validated method (GEE) to analyze these data.

A number of factors may influence the pregnancy outcomes in an insemination cycle. In a retrospective analysis of frozen-thawed donor sperm single-IUI cycles (n = 6630), age was the only factor that had a significant and independent effect on live birth rate (Brucker et al, 2009). The authors reported that the indication for using donor sperm had no effect on cumulative pregnancy rate. Similarly, in another retrospective study (n = 6139) age was the most significant determinant of pregnancy rate (Botchan et al, 2001). These 2 studies also showed no association between stimulation protocols and pregnancy rates in women using frozen-thawed donor sperm (Botchan et al, 2001). In our study there was no significant difference in mean age between the 3 protocol groups. Compared to natural cycles, use of Clomid did not alter the pregnancy rates in our study.

Our cohort study also has some weaknesses. Given the retrospective nature of our study, we could not randomly assign women to specific protocols, and one cannot be certain that there was no clinician bias in assigning women to specific protocols. However, changing from one treatment to another in subsequent cycles does reflect true clinical practice based on patient convenience and cost. We may have been unable to demonstrate a 2-fold increase in pregnancy rates with additional inseminations because of a smaller than anticipated sample size in the IUI/IUI group (the a priori determined sample size was 118 cycles). Although not statistically significant, our results show an increase in pregnancy rates of 70% for ICI/IUI (OR 1.7) and 50% for IUI/IUI (OR 1.5) when compared to single-IUI procedures, suggesting that larger studies are needed to further validate these findings. Use of donor sperm ensures adequate sperm counts. Although we found a small but significant difference in sperm parameters between groups, these differences are not clinically relevant (Johnston et al, 1994)

An important clinical consideration for patients is choosing a cost-effective protocol. Table 5 includes the approximate costs associated with the use of the 3 donor insemination protocols included in this study. The expenses are usually direct costs to the patient, as many insurance companies in the United States do not provide coverage for use of donor sperm. Taking into account the total costs the addition of a second ICI or IUI increases expense per cycle by 60%–75%. If a second insemination does not change pregnancy rates significantly, it may be more cost-effective to apply that additional expense toward the next treatment cycle, thereby increasing the number of potential treatment cycles. For example, using the total success rates for each protocol after 3 cycles (from Table 2), the success rate for the first cycle of 2 IUIs would be 13.7%, whereas the estimated cumulative success rate for 2 cycles using a single IUI would be 19% (Table 3). Two successive cycles with the 2 IUI protocol would have a cumulative success rate of 25.5%, whereas 4 cycles with a single IUI in each would have a higher cumulative success rate of 34.7% (Table 3). This would suggest that repeated cycles of single IUI would be more cost-effective than fewer cycles with 2 inseminations. Multicenter prospective studies that are appropriately powered with a large number of subjects will be needed to elucidate the most efficacious donor sperm insemination protocol.

References

Aboulghar M, Mansour R, Serour G, Abdrazek A, Amin Y, Rhodes C. Controlled ovarian hyperstimulation and intrauterine insemination for treatment of unexplained infertility should be limited to a maximum of three trials. *Fertil Steril.* 2001;75(1):88–91.

Besselink DE, Farquhar C, Kremer JA, Marjoribanks J, O'Brien P. Cervical insemination versus intra-uterine insemination of donor sperm for subfertility. *Cochrane Database Syst Rev.* 2008;(2):CD000317.

Botchan A, Hauser R, Gamzu R, Yogev L, Paz G, Yavetz H. Results of 6139 artificial insemination cycles with donor spermatozoa. *Hum Reprod*. 2001;16(11):2298–2304.

Brucker MD, Haentjens P, Evenepoel J, Devroey P, Collins J, Tournaye H. Cumulative delivery rates in different age groups after artificial insemination with donor sperm. *Hum Reprod.* 2009;24:1891–1899.

Cantineau AE, Heineman MJ, Cohlen BJ. Single versus double intrauterine insemination (IUI) in stimulated cycles for subfertile couples. *Cochrane Database Syst Rev.* 2003;(1):CD003854.

Centola GM, Mattox JH, Raubertas RF. Pregnancy rates after double versus single insemination with frozen donor semen. *Fertil Steril.* 1990;54:1089–1092.

Deary AJ, Seaton JEV, Prentice A, Morton NC, Booth AK, Smith SK. Single versus double insemination: a retrospective audit of pregnancy rates with two treatment protocols in donor insemination. *Hum Reprod*. 1997;12:1494–1496.

Goldberg JM, Mascha E, Falcone T, Attaran M. Comparison of intrauterine and intracervical insemination with frozen donor sperm: a meta-analysis. *Fertil Steril*. 1999;72(5):792–795.

Johnston RC, Kovacs GT, Lording DH, Baker HW. Correlation of semen variables and pregnancy rates for donor insemination: a 15-year retrospective. *Fertil Steril*. 1994;61(2):355–359.

Khalifa Y, Redgment CK, Tsirigotis M, Grudzinskas JG, Craft IL. The value of single versus repeated insemination in intrauterine donor insemination cycles. *Hum Reprod*. 1995;10:153–154.

Matilsky M, Geslevich Y, Ben-Ami M, Ben-Shlomo I, Weiner-Megnagi T, Shalev E. Two-day IUI treatment cycles are more successful than one-day IUI cycles when using frozen-thawed donor sperm. *J Androl*. 1998;19:603–607.

Polyzos NP, Tzioras S, Mauri D, Tatsioni A. Double versus single intrauterine insemination for unexplained infertility: a meta-analysis of randomized trials. *Fertil Steril*. 2010;94:1261–1266.

Smith JF, Eisenberg ML, Millstein SG, Nachtigall RD, Sadetsky N, Cedars MI, Katz PP; the Infertility Outcomes Program Project Group. Fertility treatments and outcomes among couples seeking fertility care: data from a prospective fertility cohort in the United States. *Fertil Steril.* 2011;95:79–84.

Zeger SL, Liang K-Y. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986;42:121–130.