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Single and double donor sperm intrauterine insemination cycles: Does double IUI increase clinical pregnancy rates?

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Abstract

Objective—To compare the pregnancy outcomes in the setting of a single versus double donor sperm intrauterine insemination (IUI) treatment cycle.

Design—Retrospective cohort study.

Setting—Large private assisted reproductive technology practice.

Patients—Donor sperm IUI recipients.

Interventions—None.

Main outcome measures—Clinical pregnancy.

Results—There were 2,486 double and 673 single donor sperm IUI cycles. The two groups were similar for age, body mass index, and the number of prior cycles. The clinical pregnancy rates were similar between the two groups (single: 16.4% versus double: 13.6%). In univariate regression analysis, age, total motile sperm (TMS), and diminished ovarian reserve (DOR) were associated with pregnancy. Generalized estimating equation models accounting for repeated measures and age, DOR and TMS and the interactions of these factors demonstrated that single and double IUI had similar odds of pregnancy (OR 1.12, 95% CI 0.96–1.44). Pregnancy rates remained similar between the two groups in matched comparison and other subgroup analyses.

Conclusion—Single and double donor IUI cycles had similar clinical pregnancy rates. This large data set did not demonstrate a benefit to routine double IUI in donor sperm cycles.

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Keywords

double intrauterine insemination; ovulation induction; donor sperm

Introduction

Artificial insemination or intrauterine insemination (IUI) remains a common first line treatment for many forms of infertility. IUI bypasses the vagina and cervix, concentrating sperm in the uterus and fallopian tubes during the peri-ovulatory period. IUI has demonstrated higher pregnancy rates of approximately 10–15 percent per IUI when combined with ovulation induction, compared to timed intercourse for some types of infertility, such as unexplained and male factor (1–3). IUI is less expensive than assisted reproductive technology (ART) cycles and generally more cost effective for many infertility diagnoses, with one ART cycle costing four-five times more than an IUI cycle (3–5). To further increase the total concentration of sperm delivered and the window of sperm exposure to the oocyte, performing IUIs on two consecutive days (double IUI) has been proposed to increase pregnancy rates. Although it has been postulated that double IUI may increase pregnancy, the current literature is controversial and lacking quality evidence that it improves outcomes (6–10).

The use of donor sperm IUI is an option for couples with severe male factor infertility, same sex couples, and single females desiring pregnancy. For couples with severe male factor infertility, donor sperm IUI provides substantial cost benefit compared to microdissection testicular sperm extraction and intracytoplasmic sperm injection ART cycles which cost approximately five times more than IUI (11). Few studies have evaluated double IUI with donor sperm. These studies have been limited by small sample sizes and provide conflicting results. The first study to evaluate a double IUI regimen was performed by Khalifa *et al.* and demonstrated no benefit to double IUI (12). In contrast, Matilsky *et al.* demonstrated higher pregnancy rates using double IUI with frozen thawed donor sperm. The double IUI clinical pregnancy rate was 17.9% per cycle versus 5% per cycle with single IUI (13). More recently, Chavkin *et al.* conducted a retrospective study of 333 donor insemination cycles. Pregnancy rates over 3 cycles were 10.2% for single IUI compared to 13.7% for double IUI ($p=0.47$) (14). While the results were not statistically significant, the authors concluded that there may be a benefit to a second insemination.

The data on the utility of double IUI using donor sperm are limited to studies with relatively small sample sizes and conflicting conclusions. The objective of this study was to evaluate the utility of frozen double donor sperm IUI to improve clinical pregnancy in a larger cohort of patients.

Materials and Methods

Study Design

This study was a retrospective cohort analysis of all donor IUI cycles at Shady Grove Fertility Reproductive Science Center from 2008–2012. There were no exclusion criteria.

Data on female age, estradiol on day of human chorionic gonadotropin (hCG) administration, total motile sperm, number of follicles greater than 14 mm on day of hCG administration, additional infertility diagnosis, type of ovulation induction and clinical pregnancy rates were collected. Information on male donor age was not available. This study was approved by the institutional review board.

Patients

All cycles using frozen thawed donor sperm IUI from 2008–2012 were included, totaling 3159 IUI cycles. No donor IUI cycles during this time frame were excluded from the study. The choice of single or double IUI was made clinically between the physician and the patient. Potential clinical factors affecting the clinical decision to use single or double IUI included the patient's diagnosis, insurance coverage mandates, the use of hCG ovulation triggering versus ovulation predictor kits, and the detection of a premature luteinizing hormone (LH) surge. Clinical use of single and double donor IUI was the decision of the individual provider. The primary infertility diagnoses were male factor infertility, same sex couple, or single female in the majority of cycles.

Processing of Donor Sperm

Methods of sperm processing did not change during the course of this study. For IUI ready frozen semen, the specimen was brought to room temperature and then to 37°C for at least 20 minutes until the sample was completely thawed. A Makler chamber was used to assess the percentage of motility, concentration (million/ml) and progression. Samples with volume greater than 0.5 mL were centrifuged for 5 minutes at 2000 revolutions per minute (RPM) and the supernatant was removed to bring the final volume to 0.3 mL with a post centrifuge count, motility, and progression performed. For frozen semen requiring processing for IUI, after assessment with a Makler chamber, at least 2 mL of Human Tubal Fluid (HTF) with 5% Serum Protein Substitute (SPS) was added to the thawed semen and mixed completely and then centrifuged for at least 5 minutes at 2000 RPM. The supernatant was removed and added to 0.3 mL of HTF/5% SPS to the pellet.

Ovulation Induction

Patients either had a natural cycle or stimulated cycle. Patients who had ovarian stimulation were given either clomiphene citrate, gonadotropins or a combination of clomiphene citrate and gonadotropins. If clinically indicated, the cycles were monitored with transvaginal ultrasound and serum estradiol measurements. When ovulation triggering was planned and the lead follicle was 18 mm, 10,000 units of intramuscular hCG was administered in the evening. Single intrauterine insemination occurred two mornings after ovulation induction (32–40 hours post hCG). Donor double IUI occurred on the two mornings following ovulation induction (two IUIs between 12–40 hours). In cycles followed with ovulation predictor kits, single IUI was performed the day after the LH surge was first detected and double IUI was performed the day of the surge and the day after. A SoftPass insemination catheter (Cook, Bloomington, Indiana) was used for the intrauterine insemination. Subjects were asked to remain supine for five minutes after the insemination procedure.

Serum hCG levels were assessed two weeks after hCG injection or LH surge detection and ultrasonographic confirmation of pregnancy was obtained in all pregnant patients. Clinical pregnancy was defined as the presence of an intrauterine gestation with fetal cardiac activity.

Statistics

The primary data analyses were performed utilizing GEE modeling with nesting for repeated cycles within a patient. Continuous variables (age, TMS) and dichotomous variables (clinical pregnancy) were assessed with the GEE models based on the type of data distribution. GEE modeling with nesting for repeated cycles within a patient and the variables age, DOR and TMS along with the interactions of these variables were utilized to further evaluate for differences in clinical pregnancy between single and double IUI. Univariate and multivariate logistic regression was used to demonstrate associations between the method of intrauterine insemination with patient characteristics, stimulation parameters, and cycle outcomes. To further control for potential undetected confounders, multiple sub-analyses were performed including the following: 1) sub-analyses restricted to 1st cycle 2) only female patients ≥ 35 years old in which there was no female co-diagnoses of infertility (eg. exclusion of polycystic ovarian syndrome (PCOS) or DOR diagnoses) 3) single versus double IUI matched by age within one year, diagnosis of DOR and TMS within one million, and 4) single versus double IUI in TMS less than and greater than 15 million. *P* values of <0.05 were considered statistically significant. Statistical analysis was performed using SPSS software (IBM, Armonk, NY).

Results

2,486 double and 673 single donor sperm IUI cycles were included in the analysis. There were 896 patients in the double IUI group and 235 patients in the single IUI group for a total of 1131 patients. The two groups were similar for age, body mass index, and the number of prior cycles (Table 1). The single IUI group had a statistically higher mean total motile sperm count in the donor sample (12 versus 10 million, $P<0.01$). In the single IUI group, 9.2% of patients had a diagnosis of diminished ovarian reserve versus 5.7% in the double IUI group ($P<0.09$). The distribution of stimulation protocols (natural cycle, clomiphene, gonadotropins, or clomiphene plus gonadotropins) was similar between the groups.

The clinical pregnancy rates were similar between the two groups (single: 16.4% versus double: 13.6%, $P=0.07$). Pregnancy rates between multiple single IUI cycles and multiple double cycles were not significant. There was no significant difference in the clinical pregnancy rates between the two groups when comparing specific ovulation induction protocols (Table 2). In univariate regression analysis, age (OR 0.92, 95%CI 0.90–0.95), TMS (OR 1.02, 95%CI 1.01–1.03) and diminished ovarian reserve (OR 0.39, 95% 0.22–0.69) significantly associated with pregnancy. A diagnosis of PCOS, female body mass index (BMI), and the number of follicles were not significantly associated with pregnancy. In multivariate regression analysis adjusting for age, total motile sperm count, diminished ovarian reserve, and type of ovulation induction, single and double IUI had similar odds of pregnancy (OR 1.28, 95%CI 0.93–1.75). The non-significance of an interaction between

both age and TMS with the type of IUI performed in the GEE model indicated that the relationship between age and TMS with pregnancy outcomes was similar regardless of the type of IUI performed. Therefore, interaction testing verified that the primary effect did not change dependent on the value of the potentially confounding variable. Generalized estimating equation modelling accounting for repeated measures and age, DOR and TMS and the interactions of these factors demonstrated that single and double IUI had similar odds of pregnancy (OR 1.12, 95% CI 0.96–1.44).

To further control for potential confounders, multiple sub-analyses were performed. To assess the effect of involving multiple repeated measures in patients undergoing multiple IUI cycles, a sub-analyses of all patient's first IUI cycle was performed. Clinical pregnancy rates for the first IUI cycles only were similar between the two groups (single IUI: 17.0% (n=235) versus double IUI: 14.4% (n=896), $P=0.36$). Sub-analyses were performed in only the highest prognosis patients. This subgroup included only the first cycle in female patients, 35 years old, and with no female co-diagnoses of infertility (eg. exclusion of polycystic ovarian syndrome or DOR diagnosis). In this good prognosis patient group, the clinical pregnancy rate was similar between the two groups (single IUI: 23.3% (n=120) versus double IUI: 18.9% (n=391), $P=0.35$). Matched sub-analyses were also performed, controlling for significant confounders of age, TMS and DOR diagnosis. In this analysis, 650 out of 673 single IUI cycles were matched to double IUI cycles by age within one year, TMS within one million and diagnosis of DOR. In 23 single IUI cycles, no double IUI cycle met the matching criteria. In this matched analyses, the clinical pregnancy rate was similar between the two groups (single IUI: 16.9% (n=650) versus double IUI: 16.1% (n=650), $P=0.79$). To assess the known positive effect of TMS greater than 15 million on clinical pregnancy, a sub-analyses was performed demonstrating similar pregnancy rates for TMS less than 15 million (single IUI: 15.8% (n=482) versus double IUI: 13.1% (n=1708), $P=0.84$) and TMS greater than 15 million (single IUI: 18.3% (n=191) versus double IUI: 14.7% (n=778), $P=0.76$).

Discussion

In this large dataset comparing single and double donor sperm IUI, there was no significant difference in clinical pregnancy rates. These findings persisted in generalized estimating equation regression models and multiple sub-group analyses accounting for repeated cycles, age, infertility diagnosis, and TMS. Our data is consistent with two other studies in showing no benefit with the addition of double IUI for donor sperm cycles (12, 14). These results are in contrast with the findings from Matilsky *et al.* which demonstrated benefit of double insemination with a clinical pregnancy rate of 17.9% per cycle versus 5% per cycle with single insemination (13). This study included 123 women undergoing ovulation induction and IUI with 80% of patients undergoing both single and double IUI during the study time period. Ninety three patients (180 cycles) underwent single IUI and 103 patients (222 cycles) underwent double IUI. Decision between single or double IUI treatment was based on the day of the week the patient was to receive hCG for ovulation induction with women receiving hCG on Sunday-Wednesday undergoing double IUI versus single IUI for hCG was administered on Thursday-Saturday. It is interesting that the pregnancy rate per cycle in the double insemination group was similar between the Matilsky study (17.9%) and the

pregnancy rates in both groups in this data set (13.6%–16.4%). The striking difference between the two studies is the very low success rate in single insemination in the Matilsky study (5%). The authors do not provide an explanation for the low success rate for single IUI, but in comparison, it is unknown how many patients had a diagnosis of DOR, and how their decision making tree for designating treatment was subject to bias. In addition, the statistical analysis in this study did not account for repeated cycles with patients undergoing up to fifteen treatment cycles.

The main strength of this study is the addition of over 3,100 donor IUI cycles to the existing literature. Post hoc power analysis was performed to estimate what difference in clinical pregnancy was excluded from this study. Using a ratio of sample sizes of 3.8:1 (double IUI: single IUI), a clinical pregnancy rate of 13.6% in the single IUI group, and a total sample size of 1131 patients, there was 95% power to detect a statistically significant difference if the alternative group proportion was 18% or higher. The exclusion of a 5% difference in clinical pregnancy and the fact that adding a second IUI increases the cost by an average of \$800 per cycle (14) questions the utility and cost effectiveness of double donor sperm IUI. The primary weakness of the study is the retrospective design, including the potential for individual physician bias in assigning treatment by single or double IUI that is not accounted for in this data set. With over three times the number of cycles in the double IUI group, there is certainly potential clinical bias in the data set. The setting of a large private ART practice with over 25 reproductive endocrinologists introduces clinical heterogeneity in the use of single and double IUI, although this could be considered strength as it reflects real world usage. Clinicians individually decided on whether to use single or double IUI and potential factors affecting the clinical decision to use single or double IUI included the patient's diagnosis, insurance coverage mandates, the use of hCG ovulation triggering versus ovulation predictor kits, and the detection of a premature LH surge. To control for potential bias, we performed generalized estimating equation models taking into account multiple cycles per patient and significant confounders and their interactions. Further, 1st cycle only and multiple sub-analyses failed to demonstrate a difference between the two groups. Despite these controls, we cannot rule out other undetected bias between the two groups that might influence the results. Ultimately, well-designed randomized controlled trials are needed to address this topic and control for the biases inherent in retrospective studies.

In conclusion, this study did not demonstrate a benefit to the routine use of double IUI in donor sperm cycles. Adding a second IUI increases the cost by an average of \$800 per cycle (14). In the absence of a demonstrable benefit and with the additional costs, the current literature does not appear to justify routine double IUI in donor sperm recipients. Given the current lack of evidence supporting a benefit of double over single donor IUI, we believe that routine clinical use of double donor IUI is not justified unless and until randomized controlled trials demonstrate a benefit to pregnancy outcomes and cost-effectiveness.

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Table 1

Demographics and treatment parameters

	Single IUI (n=673)	Double IUI (n=2486)	<i>P</i> value
Age (years)	35.5 ± 4.5	35.8 ± 4.6	0.11
Body Mass Index	26.7 ± 5.7	27.0 ± 6.1	0.22
No. of Prior cycles	1.4 ± 1.6	1.4 ± 1.6	0.41
Diminished Ovarian Reserve	9.2%	5.7%	0.09
Total Motile Sperm (10 ⁶)	12.3 ± 7.8	10.9 ± 7.1	<0.001
Stimulation Protocol			0.44
Natural Cycle (%)	47%	37%	
Clomiphene (%)	27%	26%	
Gonadotropins (%)	10%	9%	
Clomiphene + Gonadotropins (%)	16%	27%	

Table 2

Clinical Pregnancy Rate of Single IUI and Double IUI regimens divided by method of ovulation induction by Chi square analysis.

Ovulation Induction	Single IUI CPR	Double IUI CPR	<i>P</i> value
Natural	16% (n=313)	14% (n=924)	0.41
Clomiphene	17% (n=184)	14% (n=653)	0.35
Gonadotropins	17% (n=66)	17% (n=225)	0.92
Clomiphene + Gonadotropins	15% (n=110)	12% (n=683)	0.52