SHORT COMMUNICATION

TORONTO, CANADA

A prospective randomized trial of conventional *in vitro* fertilization versus intracytoplasmic sperm injection in unexplained infertility

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Purpose: To compare outcomes in patients with unexplained infertility undergoing conventional *in vitro* fertilization (IVF) versus intracytoplasmic sperm injection (ICSI).

Methods: Sixty women with unexplained infertility in a Canadian tertiary-level clinic were randomized to IVF or ICSI. Subjects underwent downregulation with gonadotropin-releasing hormone agonist prior to initiation of recombinant human follicle-stimulating hormone. The primary outcome measure was fertilization rate. Secondary outcomes included implantation rate, embryo quality, clinical pregnancy rate, and live birth rate.

Results: There was no statistically significant difference in fertilization rate (77.2% IVF vs. 82.4% ICSI), implantation rate (38.2% IVF vs. 44.4% ICSI), clinical pregnancy rate (50% in each group), or live birth rate (46.7% IVF vs. 50% ICSI). There were two cases of failed fertilization in the IVF group. There was no significant difference in embryo quality between groups.

Conclusions: There were no differences in clinical outcomes associated with IVF versus ICSI in the treatment of unexplained infertility.

KEY WORDS: Intracytoplasmic sperm injection; *in vitro* fertilization; unexplained infertility.

INTRODUCTION

Couples diagnosed with unexplained infertility have traditionally been offered treatment options such as ovulation induction or *in vitro* fertilization (IVF). In 1992, intracytoplasmic sperm injection (ICSI) emerged as an effective treatment for male factor infertility. Although ICSI may lead

to an increased likelihood of fertilization (1,2), there is limited evidence about its effectiveness among those with unexplained infertility. The objective of this prospective randomized trial is to determine if ICSI improves outcome over conventional IVF in couples with unexplained infertility.

MATERIALS AND METHODS

Sixty patients with unexplained infertility were randomized to either IVF or ICSI. The inclusion criteria was female age 18–40 years, regular ovulatory menstrual cycles, day #3 estradiol (E_2) < 200 pmol/L, follicle stimulating hormone (FSH) < 15 IU/L, luteinizing hormone (LH) < 8 IU/L, normal thyroid stimulating hormone, ≥ 3 previous intrauterine insemination (IUI) cycles with clomiphene citrate or gonadotropins, normal uterine cavity, fallopian tubes and presence of both ovaries, normal ultrasound (US), and previous laparoscopy excluding stage III or IV endometriosis. All male partners had a normal semen analysis by WHO criteria (3). Ethical approval was obtained from the institutional review board and all patients provided written informed consent.

Pituitary downregulation was achieved with luteal phase gonadotropin-releasing hormone (GnRH) agonist (Lupron, TAP Pharmaceuticals, St. Louis, Missouri, USA or Suprefact, Hoechst AG, Frankfurt, Germany). Ovarian stimulation with Gonal-F injection was started after confirmation of downregulation and cycle monitoring was performed by US and serum E_2 . Treatment with Gonal-F was discontinued in cases of poor ovarian response as defined by a plateau or drop in serum E_2 after three consecutive days at the maximum Gonal-F dose of 450 IU/day. When the diameter of the largest follicle was ≥ 18 mm, with at least two other follicles ≥ 16 mm, human chorionic gonadotropin (Profasi; Serono Canada Inc., Oakville, Ontario, Canada) was administered followed by transvaginal oocyte retrieval 35 h later. Insemination for IVF or ICSI was performed using sperm collected on the day of retrieval. The best embryos (maximum of four) were transferred on day #3 postretrieval. Profasi injections or natural progesterone vaginal suppositories were used for luteal support. Serum β hCG was assessed 16 days postembryo transfer, followed by US at 6–7 weeks gestation.

Statistical Analysis

The primary outcome measure was the difference in fertilization rates between IVF versus ICSI. Fertilization rate was defined as the proportion of mature oocytes (IVF group) or metaphase II oocytes (ICSI group) that fertilized. Secondary outcomes included differences in implantation rate, embryo quality, clinical pregnancy rate, and live birth rate. Implantation rate was defined as the number of gestational sacs on US at 6–7 weeks gestation per number of embryos transferred. Clinical pregnancy rate was defined as the proportion of patients with positive cardiac activity on US at 6–7 weeks gestation over the total patients in each group. Live birth rate was the number of pregnancies resulting in a live birth among all study participants in each group.

Data was analyzed using SPSS/PC version 10.0. The data analysis included descriptive techniques (frequencies), bivariate analysis (χ^2) and comparisons of means, with $p < 0.05$ defined as significant. When there was a gradient in the data, the Mantel–Haenszel test for linear trend was used. Intention to treat analysis was conducted with all participants included in the denominator.

RESULTS

Sixty patients with unexplained infertility, recruited between 1997 and 2001, were equally randomized to IVF or ICSI with no baseline differences between groups (Table I). Of the 30 IVF cycles started, one patient was canceled for poor stimulation, three patients were found to have abnormal sperm parameters (3) on the day of oocyte retrieval and ICSI was performed, and two patients had total fertilization failure requiring rescue ICSI. Of the 30 patients randomized to ICSI, four cases were canceled for poor response.

Using intention to treat analysis, there were no differences between IVF or ICSI in the duration of stimulation, peak E_2 , oocytes retrieved, and oocyte or embryo quality, with the exception of oocytes that received a score of 3 out of 4. No differences were observed in fertilization, implantation, clinical pregnancy, or live birth rates (Table II).

A secondary analysis of participants who proceeded to oocyte retrieval without any protocol deviations (IVF = 24, ICSI = 26) revealed no statistically significant difference in fertilization rates (IVF 77.3% vs. ICSI 82.4%, $p = 0.3$), implantation

Table I. Baseline Characteristics of All Study Participants

Baseline characteristic	IVF (<i>n</i> = 30)	ICSI (<i>n</i> = 30)
Age (years)	33.0 ± 3.6	33.7 ± 2.1
BMI (kg/m ²)	24.5 ± 3.4	24.01 ± 4.05
Duration of infertility (month)	57.2 ± 35.5	64.5 ± 28.2
Day 3 FSH (IU/L) ^a	6.2 ± 1.4	6.5 ± 1.8
Day 3 E_2 (pmol/L) ^b	136.6 ± 70.4	166.8 ± 99.0
Total sperm count ($\times 10^6$)	246 ± 222.2	275 ± 136.7
Sperm density (10^6 /mL)	74.9 ± 69.58	80.9 ± 52.26
Sperm motility (% rapid and slow)	50.2 ± 7.2	52.1 ± 7.0
Sperm morphology (% normal forms)	31.9 ± 11.7	34.5 ± 9.7

Note. All data values expressed as mean ± standard deviation. $p > 0.05$ for all values compared.

^aConversion factor: mIU/mL $\times 1.0$ = IU/mL.

^bConversion factor: pg/mL $\times 3.671$ = pmol/L.

rate (IVF 39.1% vs. ICSI 44.4%, $p = 0.7$), clinical pregnancy rate (IVF 54.2% vs. ICSI 57.7%, $p = 0.8$), or live birth rate (IVF 54.2% vs. ICSI 57.7%, $p = 0.8$).

DISCUSSION

The results of this trial suggest that there are no significant differences in any of the outcome

Table II. Details of Treatment Cycles for All Study Participants

	IVF (<i>n</i> = 30)	ICSI (<i>n</i> = 30)	<i>p</i>
Stimulation duration (days)	12	12	NS
E_2 maximum (pmol/L) ^a	7633.1	8073.7	NS
No. of oocytes retrieved per patient	19.1	20.8	NS
Oocytes score 1 (% , SE)	86.0 (2.0)	82.0 (1.8)	NS
Oocytes score 2 (% , SE)	11.0 (2.0)	8.0 (1.0)	NS
Oocytes score 3 (% , SE)	0.7 (4.0)	8.0 (8.0)	0.001
Oocytes score 4 (% , SE)	2.0 (4.0)	1.0 (4.0)	NS
Total no. of embryos obtained per patient	10.2	11.5	NS
No. of embryos transferred per patient	2.7	2.4	NS
Embryos transferred score 1 (% , SE)	35.9 (7.7)	28.9 (7.9)	NS
Embryos transferred score 2 (% , SE)	43.7 (7.6)	45.5 (8.4)	NS
Embryos transferred score 3 (% , SE)	19.3 (6.7)	24.4 (3.7)	NS
Embryos transferred score 4 (% , SE)	1.1 (1.1)	1.3 (1.3)	NS
Fertilization rate (%)	77.2	82.4	NS
Implantation rate (%)	38.2	44.4	NS
Clinical pregnancy rate (%)	50.0	50.0	NS
Live birth rate (%)	46.7	50.0	NS

Note. All data values expressed as means; NS: not significant.

^aConversion factor: pg/mL $\times 3.671$ = pmol/L.

measures—fertilization rate, implantation rate, embryo quality, clinical pregnancy rate, or live birth rate—between those undergoing IVF versus ICSI for unexplained infertility. As noted by others, this data suggests that ICSI does not improve outcomes over a standard IVF protocol that uses rescue ICSI in cases of total fertilization failure with regard to implantation and pregnancy rates (4,5).

In a study of nonmale factor infertility, ICSI increased the fertilization rate per oocyte injected compared to conventionally inseminated oocytes, but no information on the comparability of quality and maturity of oocytes between study groups were reported (4). Our study outcomes, which reflect those associated with mature oocytes, revealed no statistical difference in fertilization rates. However, the 5% difference between IVF and ICSI fertilization rates may be of some clinical relevance.

Earlier trials comparing conventional IVF to ICSI in sibling oocytes of couples with unexplained infertility found no difference in fertilization rates although they noted cases of total fertilization failure with the use of IVF (11.4% and 22.7%) but not ICSI (6, 7). More recently in a randomized controlled trial of IVF versus ICSI, there was a single case of failed fertilization in the IVF group ($n = 48$) and none in the ICSI group ($n = 52$) among patients with unexplained infertility (8). In our study, there were two cases (6.7%) of fertilization failure in the IVF group and none in the ICSI group. One would estimate from our data that at least 15 cases would need to be treated with ICSI to avoid one case of failed fertilization. Although these are all small sample sizes, the finding of a reduction in fertilization failure warrants additional assessment.

The theoretical concerns of increased chromosomal anomalies, poorer embryo development, and transmission of exogenous DNA by spermatozoa injection (8–17) need to be considered. Ultimately, the benefits along with the safety concerns, costs, and inconveniences must be weighed with the indication for ICSI in unexplained infertility. Despite our small sample size, the results of our prospective randomized trial do not support the routine use of ICSI for patients with unexplained infertility. What remains unclear is the true efficacy of ICSI, the long-term outcome of these children, and the potential economic and social benefits of conventional IVF compared to ICSI in unexplained infertility.

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