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Effect of Tubal and Pelvic Pathology on Uterine Receptivity and Success in Intracytoplasmic Sperm Injection

A Clinical Study

Key Words

Intracytoplasmic sperm
injection
Tubal pathology
Treated endometriosis
Tubal embryo transfer
Pregnancy outcome

Abstract

Objective: To evaluate the effect of pelvic pathology on pregnancy outcome of couples with male factor infertility undergoing intracytoplasmic sperm injection (ICSI) and tubal embryo transfer (TET). **Design:** Clinical study of patients who underwent ICSI for poor sperm parameters. **Setting:** Tertiary care academic center. **Patients:** Twenty-six women with normal pelvis (group A) were matched according to age, stimulation protocol, number of transferred embryos, and number of cycles with 26 patients treated for stage 1 endometriosis (group B), and 26 patients with pelvic disease and at least one patent tube (group C). **Main Outcome Measure:** Pregnancy/cycle, pregnancy/patient, implantation rate and miscarriage rate. **Results:** Patients with normal pelvis undergoing ICSI and those with treated mild endometriosis demonstrated significantly better embryo implantation and miscarriage rates than ICSI patients with minimal tubal disease. Ongoing pregnancy rate was 50% for patients with normal pelvis and treated endometriosis groups and 30% for women with tubal pathology. The miscarriage rate of patients with tubal disease (33%) was significantly higher than that of the other two groups (14%). **Conclusion:** Treated mild endometriosis does not affect the outcome in ICSI patients undergoing TET when compared to women with normal pelvic findings, but the presence of tubal disease might affect the pregnancy outcome.

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Introduction

Severe tubal disease was the initial indication for in vitro fertilization and embryo transfer (IVF-ET). With improvements in IVF-ET pregnancy rates, those indications were expanded to include pelvic endometriosis, unexplained infertility, ovulatory dysfunction, immunologic infertility as well as male factor infertility. Unfortunately, implantation rate and pregnancy rates in severe male factor infertility remained very low with very low oocyte fertilization rates. Intracytoplasmic sperm injection (ICSI) [1] is heralded as a major breakthrough in the treatment of male factor infertility. Even with a few motile sperms, each injected into a mature human oocyte, fertilization could be achieved [2–4]. If the male factor infertility is corrected with ICSI, a high pregnancy rate should be achieved in healthy young women undergoing ICSI.

Endometriosis may affect oocyte fertilizability and subsequent implantations [5]. Furthermore, peritoneal fluid of patients with endometriosis can impair sperm function [6], or be embryotoxic [7]. However, some studies have shown similar outcome of patients with endometriosis compared to tubal factor infertility patients treated with IVF [8, 9].

The purpose of this study is to evaluate the pregnancy rates and implantation rates of women with treated minimal to mild endometriosis and patients with pelvic pathology undergoing ICSI and tubal embryo transfer (TET) for male factor infertility, and to compare the results to the pregnancy rates and implantation rates of women with subtle tubal disease.

Materials and Methods

Twenty-six women with normal pelvic anatomy (group A) were matched according to age, parity, socioeconomic status, number of transfer cycles, and num-

ber of embryos transferred, with 26 women treated with laser laparoscopy (group B) for mild endometriosis [10], and 26 women with subtle tubal disease [11, 12] such as fimbrial agglutination or phimosis, tubal diverticulae, short fimbria, and/or tubal adhesions (group C) with at least one patent tube. IVF for ICSI was performed in patients with very low fertilization (<15% in 10 oocytes) in a previous IVF cycle, in couples with concentration of motile sperm <5 million in the total ejaculate, and in couples with less than 4% normal morphology in the husband's sperm. Patients with hydrosalpinx were excluded from the study [13, 14].

The pelvic status of all patients in this study was documented by laparoscopy, and a second laparoscopy was performed at the time of TET. All endometriosis patients were disease-free at the time of TET.

All patients received GnRH agonist in the midluteal phase followed by intramuscular administration of human menopausal gonadotropin (Pergonal, Serono Laboratories, Inc., Randolph, Mass., USA) starting on the 3rd day of the menstrual cycle [15]. When three or more follicles showed a mean diameter ≥ 18 mm, and serum estradiol >800 pg/ml (2,800 pmol/l), 10,000 IU of human chorionic gonadotropin (hCG) was administered. Thirty-six hours later, follicular aspiration was performed using ultrasound-guided transvaginal aspiration.

Both groups had similar luteal phase support with oral progesterone of 600 mg administered daily from the day of retrieval, and 50 mg i.m. administered every other day starting after the day of transfer. The latter dosage was increased to 50 mg i.m. daily, 1 week later for 6 weeks. Five thousand international units of hCG was administered once, 1 week post retrieval.

Oocytes were immediately identified, rinsed free from blood, scored and transferred into microdrops of Ham's F-10 supplemented with Plasmatein. Mature oocytes were stripped off their cumulus-corona complex by using 80 IU/ml hyaluronidase (Type VIII No. H3757; Sigma, St. Louis, Mo., USA) prepared fresh in HTF-Hepes solution. Only mature oocytes were used for ICSI [16].

The injection and holding pipettes were prepared by pulling glass capillaries on the Sutter puller P-87 (Drummond; Sutter Industries, Novato, Calif., USA). The sperm injection pipette was cut on a microforge (MF-9, Narashige Instrument, Tokoy, Japan) at an outer diameter of 7–8 μ m and inner diameter of 4 μ m. A bevel of 48–50° was made on a microgrinder (EG-4, Narashige). A sharp spike was produced by a 'gentle touch and pull' method on the microforge filament. By

Table 1. The age, number of ICSI cycles, and number of embryos transferred of the three groups

	Normal pelvis (A)	Mild endo- metriosis (B)	Tubal disease (C)
Age*	32.54	33.27	32.77
Transfer cycles*	34	37	32
Cycles/patient*	1.3	1.4	1.2
Embryos transferred	177	207	180
Embryos transferred/cycle*	5.2	5.6	5.6

* $p > 0.05$ between the three groups.

positioning the heater filament close to the shaft of the pipette (5–8 mm from the tip) an angle of 45° was produced.

The micromanipulation system NT88 (Narashige, USA) was used for sperm injection, and for oocyte holding, IM-6 microinjectors were utilized. They were fitted with 800-μl glass microsyringes. The glass syringe was filled with light mineral oil (Sigma, No. M8410). The Teflon tubing (CT-1), which connects the syringe to the glass micro-pipette holder (H1-4), was also filled with oil. Care was taken to remove all air bubbles from the system before ICSI was performed.

Both the injection and the holding pipettes were in the same plane when the sperm injection was performed. Both the stereo and the inverted microscopes were fitted with heated stages (Cryogenic Concepts, Allentown, Pa., USA).

A morphologically normal-looking motile sperm was immobilized by pressing the mid piece or tail region with the tip of the injection pipette. This immobile sperm was drawn tail first into the pipette. Oocytes were then injected with a single spermatozoon [1]. ET was performed 48–72 h post retrieval. TET was performed when at least one normal tube was encountered.

The Institutional Review Board approval was obtained. Clinical pregnancy was regarded after the gestational sac was visualized. Ongoing pregnancy was regarded after 20 weeks of gestation.

While Student's t test was used for the comparison of the difference between the means of two continuous variables, the normal Z test was used to determine the significance of differences between two proportions, and the comparison between two ratios was effected through the normal ratio test [17].

Results

Table 1 compares the clinical characteristics of the three groups. The differences in age, number of transfer cycles and cycles per patient, number of embryos transferred and embryos transferred per cycle were not statistically significant at the 95% confidence interval. Therefore, these groups were statistically comparable.

Table 2 compares the clinical outcomes of these three groups. The ongoing pregnancy rate after ICSI and TET in women with a normal pelvis (56%) was similar to that of the treated endometriosis group (B, 48.6%), and both results were significantly greater ($p < 0.05$) than those obtained in women with early tubal disease (25%). Similarly, the implantation rates of groups A and B (18.6 and 15.4%, respectively) were significantly higher than that of group C (8.9%).

As can be seen in table 2, we did not notice any increase in spontaneous abortion in the endometriosis group when compared to the normal pelvis group. Both however were significantly lower than that of patients with tubal disease. All of our endometriosis patients were in the mild stage and all of them received treatment in the past. The miscarriage rate in women with minimal tubal disease (33%) was significantly higher than that

Table 2. Clinical outcomes of the three groups

	Normal pelvis (A)	Mild endometriosis (B)	Tubal disease (C)
Implantation rate (%)	33/177 (19)	32/207 (15)	16/180 (9) ^{a, b}
Pregnancy/cycle (%)	22/34 (65)	21/37 (57)	12/32 (38)
Ongoing/cycle (%)	19/34 (56)	18/37 (49)	8/32 (25) ^{a, b}
Miscarriage rate (%)	3/22 (14)	3/21 (14)	3/21 (14)

^a p < 0.05 group A vs. group C.
^b p < 0.05 group B vs. group C.
Differences between groups A and B were not statistically significant.

of group A (13.2%) and group B (14.2%). The differences in outcomes between groups A and B were not statistically significant. One tubal pregnancy was encountered in group C, and none in the other two groups.

Discussion

Severe oligoasthenospermia is usually associated with a very low fertilization rate when conventional IVF is performed. This obviously results in a very low pregnancy rate with IVF-ET. Correcting the fertilization problem using ICSI can result in a high pregnancy rate when the female pelvis is normal. Several reports have appeared in the literature showing lower pregnancy rates with conventional IVF in women with severe tubal disease (hydrosalpinx) [13, 14]. We have previously reported lower pregnancy rates when GIFT was performed on women with subtle tubal abnormalities compared to women with normal tubes [11]: Such abnormalities included tubal diverticulae, kinking, convolutions or fimbrial agglutination.

In this study, we found high pregnancy rates when normal dividing embryos obtained after ICSI were transferred into the fallopian tubes of women whose husbands suffer from severe oligoasthenospermia.

Patients of groups A and B had an implantation rate of 18.6 and 15.4%, respectively, both significantly higher than group C's (8.9%). This may be due to defective interaction between the embryos and the tubal lumen, leading to poor embryo development, or defective muscularis leading to poor peristalsis. It is also possible that scarred tubes produce embryotoxic substances, or conversely, do not produce factor(s) necessary for embryo survival. ICSI and TET, however, still offered these patients a 25% chance of a viable pregnancy.

Pellicer et al. [5] have suggested that endometriosis may affect oocyte quality, resulting in embryos of a lower quality that do not implant as well. We did not observe this phenomenon, and if it is present, ICSI might have corrected it. It is also possible that treatment of endometriosis improved that 'defect'. Matson and Yovich [8] and Olivennes et al. [18] have found that the outcome of patients undergoing IVF-ET is not different among patients with mild to moderate endometriosis and those with tubal disease. Wardle et al. [9] have found that untreated endometriosis reduces fertilization rates. They later reported improved outcome if the endometriosis was treated, with a success rate equaling that of patients with tubal disease, whom he used as controls. Miller et al. [19] found that serum

from women with endometriosis inhibited fertilization and early embryo development in murine, and that improvement was noted after laser laparoscopy treatment of endometriosis. In this study, patients with treated endometriosis did significantly better than those with tubal disease. It is possible that embryo transfer into healthy tubes confers an advantage to embryo survival. It may be worthwhile treating mild endometriosis with laser laparoscopy since this may improve the pregnancy rate.

In conclusion, subtle tubal disease appears to adversely affect the outcomes of assisted

reproductive technology, an extreme example being patients with hydrosalpinges [13, 14]. Patients undergoing such procedures should be counselled accordingly when TET is utilized. Moreover, ICSI can produce high pregnancy rates in couples with male infertility when the woman's pelvic organs are normal. Treated endometriosis does not seem to adversely affect the outcome of ICSI with TET, which is in fact very comparable to patients with normal pelvic anatomy. Women with subtle tubal pathology may benefit from uterine embryo transfer instead of TET, since tubal receptivity may be a factor.

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