COMPARISON OF ZYGOTE INTRAFALLOPIAN TRANSFER AND INTRAUTERINE EMBRYO TRANSFER FOR MALE-FACTOR INFERTILITY AFTER INTRACYTOPLASMIC SPERM INJECTION

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SUMMARY

Objective: In vitro fertilization and embryo transfer (IVF-ET) have been increasingly used for treating male-factor infertility. However, zygote intrafallopian transfer (ZIFT) allows early embryo development to occur within the natural environment of the tubal lumen. The purpose of this study was to analyze whether the mode of embryo transfer, ZIFT versus intrauterine ET, affected the pregnancy outcome in the IVF cycle after intracytoplasmic sperm injection (ICSI) for the treatment of male-factor infertility.

Materials and Methods: A total of 140 ICSI procedures (69 ET, 71 ZIFT) were analyzed. A maximum of four cleaving embryos were transferred into the fallopian tube or uterine cavity 48 and 72 hours after oocyte retrieval, respectively. Several variables, including mean age, IVF cycle day 2 hormone levels, peak E2 level, number of oocytes retrieved, number of embryos transferred, endometrial thickness, pulsatility index and resistance index of the uterine artery, and clinical pregnancy rate, were analyzed.

Results: The clinical pregnancy rate for ET was 25.4% versus 24.7% for ZIFT. There was no significant difference between the two groups in the other variables, except for mean age.

Conclusions: The data presented in this report demonstrate that there was no therapeutic improvement associated with the increased complexity of ZIFT as compared with intrauterine ET after ICSI for the treatment of male-factor infertility. With the advent of improvements in culture techniques in the IVF laboratory, intrauterine ET remains the technique of choice. [Taiwanese J Obstet Gynecol 2004;43(1):25-28]

Key Words: in vitro fertilization, embryo transfer, zygote intrafallopian transfer, intracytoplasmic sperm injection

Introduction

The human fallopian tube is a site of active muscular contraction, clinical activity, and chemokine secretion and reception [1–3]. In this regard, it may be considered an active participant in fertilization and early embryogenesis. In 1986, Devroey et al [4] reported the first pregnancy from a zygote intrafallopian transfer (ZIFT) procedure. This technique was aimed initially at treating couples with underlying male-factor infertility, and who have undergone unsuccessful gamete intrafallopian transfer (GIFT) procedures, but ZIFT has since been expanded to treat all infertility etiologies.

It has been suggested that the transfer of a cleavage stage embryo into the fallopian tube is more physiologic than replacement into the uterus, and provides the most appropriate embryo culture conditions [5–7]. There are several additional theoretical advantages to ZIFT. The transfer of the zygote at the ampullary portion of the tube would allow further development before entry into the uterine cavity, and the zygote could then enter the uterus at a more advanced stage of development or in greater synchronization with the uterus. The pre-
Analysis was generally conducted 1 to 2 months prior to investigation results for the female partner. Semen with longstanding infertility, and normal infertility semen analyses on two or more occasions, combined infertility was defined as the persistence of abnormal male factors of infertility were excluded. Male-factor longstanding male-factor infertility. Couples with female partners had a basic infertility work-up. The ovulatory status was assessed using a basal body temperature chart and endocrinologic profile, and the tubal status by hysterosalpingography (HSG) or chromolaparoscopy. If an additional factor was found at this work-up, the couple was excluded from the study.

In male-factor infertility, information regarding fertilization is of utmost interest, and ZIFT allows confirmation of fertilization before transfer, and allows the exclusion of polyembryos.

There are, however, several disadvantages to ZIFT, such as the need for general anesthesia, laparoscopy, and a longer postoperative recovery time. The procedure entails greater medical risk, is expensive for the patient (due to the laparoscopic procedure), and imposes significant logistic difficulties for the center. There is also a potentially greater risk of ectopic tubal pregnancy [8].

In vitro fertilization and embryo transfer (IVF-ET) is an important treatment option for many etiologies of infertility, and has been increasingly used for treating male-factor infertility. As we have come to better understand the requirements of early-stage embryos and devised more physiologic culture media, clinical IVF success rates have improved. Furthermore, intracytoplasmic sperm injection (ICSI) has revolutionized the treatment of male-factor infertility, making it possible to achieve fertilization and pregnancy even in the most severe cases of male-factor infertility cases [9]. Published reports of success rates indicate clinical pregnancy rates of approximately 20–40% when ICSI is used in IVF cycles [10]. The purpose of this study was to analyze whether the mode of embryo transfer, ZIFT versus intrauterine ET, affected the pregnancy outcome in the IVF cycle after ICSI for the treatment of male-factor infertility.

Patients and Methods

Patients

Between January 1999 and May 2002, all couples undergoing transvaginal oocyte retrieval for nontubal-factor infertility were offered the opportunity to select the use of ZIFT versus intrauterine ET. Informed consent was obtained from all the couples, and the study was approved by the Institutional Review Board of the National Cheng Kung University Hospital, Taiwan.

A total of 140 couples with male-factor infertility, and undergoing ICSI procedures, were analyzed. Inclusion criteria allowed only first-trial couples with longstanding male-factor infertility. Couples with female factors of infertility were excluded. Male-factor infertility was defined as the persistence of abnormal semen analyses on two or more occasions, combined with longstanding infertility, and normal infertility investigation results for the female partner. Semen analysis was generally conducted 1 to 2 months prior to the IVF cycle, following World Health Organization criteria [11], with results considered abnormal if the count was less than $20 \times 10^6$ mL, if the progressive motility in the sample was below 50% or if the percentage of sperm with normal morphology using strict criteria was less than 4% [12]. Affected males generally had two or more suboptimal semen parameters.

All patients underwent the previously described standard long protocol, consisting of pretreatment with a gonadotropin-releasing hormone analog (GnRH-a) (Lupron; Abbott Laboratories, North Chicago, Illinois, USA), followed by stimulation with follicle stimulating hormone (FSH) (Metrodin-HP; Serono SA, Geneva, Switzerland) and human menopausal gonadotropin (HMG) (Pergonal; Serono SA) for controlled ovarian stimulation [13]. All the recruited subjects had been treated with oral contraceptive pills (1 tab per day for 21 days) in the previous menstrual cycle. Beginning from day 21 of the previous cycle, pituitary down-regulation was accomplished with 1 mg/day subcutaneous GnRH-a. The dose was reduced to 0.5 mg/day from day 2 of the IVF cycle until the day prior to human chorionic gonadotropin (hCG) administration. From day 3 of the ensuing menses, three ampoules (amps) of Metrodin-HP were administered daily for 4 days. This was then shifted to Metrodin-HP 1 amp + HMG in various doses (2–3 amps) daily. Blood samples were taken for estradiol analysis on day 2, day 7, and daily from day 9 of the IVF cycle. When at least one follicle had a diameter of $\geq 18$ mm, and the serum estradiol level was $\geq 200$ pg/mL for each follicle $>14$ mm in diameter, hCG (Profasi; Serono SA) 10,000 IU was administered intramuscularly, and oocytes were recovered 34 hours later under transvaginal ultrasound guidance.

Oocytes were collected (defined as D0) and trimmed of excess cumulus cells using 27-G needles, then treated with 80 IU/mL hyaluronidase (type VIII; Sigma Chemical Co, St Louis, MO, USA) for 30 to 60 seconds to completely remove the cumulus cells. ICSI was carried out using commercially available injection pipettes (Humana catheter). The D3 ET transfers were performed by laparoscopy, using a Cook Humana catheter. The D3 ET transfers were performed...
using a Labtect or Wallace catheter. Patients were placed on progesterone and hCG booster injections for luteal-phase support. Clinical pregnancy was defined as the presence of at least one observed gestational sac.

Data were collected on patient age and IVF cycle day 2 serum levels of estradiol, progesterone, FSH, and luteinizing hormone (LH); serum levels of estradiol on hCG day; total medication dosage of gonadotropin; number of mature oocytes collected; number of embryos transferred; endometrial thickness; uterine artery blood flow velocity indices (pulsatility index, PI and resistance index, RI); and the clinical pregnancy rate for both ZIFT and intrauterine ET after IVF with ICSI.

Statistics
Data are presented as mean ± standard deviation (SD). Comparisons between the two groups were performed using the Mann-Whitney U-test or one-way analysis of variance as appropriate. A p value less than 0.05 was considered statistically significant.

Results
One hundred and forty couples were selected for our study. The husbands all suffered from idiopathic male-factor infertility (since no obvious cause for their problem had been identified). The mean age ± SD of the women in the ET group (n = 69) was 33.6 ± 5.1 years, and that of the women in the ZIFT group (n = 71) was 31.3 ± 3.9 years (p < 0.05).

The basic IVF cycle day 2 hormone profile, including FSH, LH, E2, and progesterone, showed no significant differences between the two groups (Table). After controlled ovarian hyperstimulation, there was a tendency toward fewer oocytes retrieved and a slightly higher gonadotropin dosage in the ET group (p > 0.05). There were no significant differences in the number of embryo replacements, endometrial thickness, or uterine artery blood flow velocity indices (PI and RI) between the ET and ZIFT groups (Table). The clinical pregnancy rate for ET was 25.4%, versus 24.7% for ZIFT; the difference was not significant.

Discussion
The pregnancy rates after the two transfer procedures revealed no significant differences. Various factors related to the procedures themselves or related to the indication, i.e. male-factor infertility, may explain this finding. In ZIFT, the normal tubal environment could have been altered at the time of transfer, e.g. by tissue trauma after the replacement, by exposure to the blood in the peritoneal cavity from the ovum pick-up, by the light or pneumoperitoneum used for laparoscopy, or even by anesthesia. Another point is the status of the oviduct itself. Occult intraluminal adhesions and fibrosis or deciliation of the tubal mucosa are not fully assessed by HSG or laparoscopy. Tubal patency does not imply tubal functionality [14]. In most retrospective studies, increased pregnancy and implantation rates result from

| Table. Comparison of variables between the ET and ZIFT groups |
|-----------------|-----------------|-----------------|-----------------|
|                  | ET (n = 69)     | ZIFT (n = 71)   | p               |
| Age (yr)         | 33.6 ± 5.1      | 31.3 ± 3.9      | <0.05           |
| D2 FSH (mIU/mL)  | 3.64 ± 3.13     | 3.08 ± 1.58     | NS              |
| D2 LH (mIU/mL)   | 2.61 ± 5.50     | 2.49 ± 1.99     | NS              |
| D2 E2 (pg/mL)    | 38.78 ± 19.62   | 38.46 ± 27.16   | NS              |
| D2 Progesterone (ng/mL) | 0.65 ± 0.33 | 0.63 ± 0.29 | NS              |
| COH              |                |                |                 |
| Ovulation induction (d) | 10.1 ± 1.3     | 10.0 ± 1.5     | NS              |
| Gonadotropin dosage (amps) | 28.3 ± 5.9     | 26.8 ± 5.8     | NS              |
| E2 on hCG day (pg/mL) | 2229.29 ± 1305.26 | 2524.85 ± 1372.73 | NS            |
| Oocytes retrieved (n) | 12.1 ± 9.1      | 14.8 ± 9.7     | NS              |
| Embryo replacements (n) | 3.6 ± 1.2       | 3.2 ± 1.2      | NS              |
| Endometrial thickness (mm) | 11.24 ± 2.71   | 11.16 ± 2.57   | NS              |
| PI (uterine artery)  | 2.20 ± 0.54     | 2.28 ± 0.42    | NS              |
| RI (uterine artery)  | 0.82 ± 0.08     | 0.83 ± 0.05    | NS              |
| Pregnancy rate (%)  | 25.4            | 24.7            | NS              |

ET = embryo transfer; ZIFT = zygote intrafallopian transfer; FSH = follicle stimulating hormone; NS = not significant; LH = luteinizing hormone; COH = controlled ovarian hyperstimulation; hCG = human chorionic gonadotropin; PI = pulsatility index; RI = resistance index.
In this study, only couples with male-factor infertility were selected, and IVF was restricted to the ICSI procedure, so we could compare the different modes of transfer after the confirmation of cleaving embryos. Our results, in contrast to those of other retrospective studies [5–7], do not show any therapeutic advantage to ZIFT over intrauterine ET in this category of couples. Furthermore, the ZIFT procedure requires laparoscopy as well as general anesthesia, is longer in duration, and involves inevitable hospitalization. Its cost is therefore higher than that of IVF-ET.

Several studies have also revealed no therapeutic advantage to ZIFT over IVF-ET in male-factor or nontubal-factor infertility, in terms of reproductive outcome or economic benefit [14,19,20], but no other retrospective study compares ZIFT and intrauterine ET for only couples with male-factor infertility undergoing ICSI procedures. Currently, we cannot demonstrate a significant advantage to the use of this more expensive, inconvenient, and invasive technique. With the advent of improvements in culture techniques in the IVF laboratory, intrauterine ET remains the technique of choice. For ZIFT to become a viable treatment option, subpopulations in which its use may be of benefit will need to be identified.

References


