The Pregnancy Rates - A Retrospective Comparison of Tubal and Uterine Embryo Transfers

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Abstract

Tubal embryo transfer (TET), which involves an embryo transfer *via* the uterine tube, has a possible advantage over uterine embryo transfer (UET) due to more natural timing of embryo exposure to the uterine cavity. This study was carried out to evaluate the pregnancy rate of TET *versus* UET. Eight hundred and ninety-seven consecutive patients who underwent embryo transfers from July 1997 to June 1999 in Bielefelder Institut fuer Fortpflanzungs-medizin (BIF.), Germany were included in this study. Two hundred and eighty-six pregnancies were achieved in 167 cases (31.4%) after TET and 119 cases (24.6%) after UET. The abortion rate of the TET group was 12.0 per cent while that of the UET group was 23.3 per cent. Our results showed that TET has a significantly increased clinical pregnancy rate and significantly decreased abortion rate. There is an advantage in transferring embryos to the fallopian tube in infertile couples with male factor infertility and unexplained infertility. We recommend TET as the first choice for embryo transfer in infertile couples with patent fallopian tubes and with no evidence of pelvic adhesion and/or endometriosis.

Key word : Tubal Embryo Transfer (TET), Transcervical Transfer of Embryo to the Uterus, or Uterine Embryo Transfer (UET), Clinical Pregnancy

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Assisted reproductive technologies have been used to treat couples with a variety of infertility diagnoses. However, a classic one is tubal factor infertility. Following the introduction of intracytoplasmic sperm injection (ICSI), more cases of male infertility can be treated and the number of cases with this indication has increased dramatically. Consequently, the number of patients

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with patent tubes has increased. Many programs have now achieved a delivery / retrieval pregnancy rate of more than 25 per cent. The method of choice can be done on the basis of many factors including the chance of success. The importance in terms of choosing a technique is consideration of which program, tubal or uterine transfer, has achieved the best results in women with male factor infertility and unexplained infertility[1]. From previous reports, the transfer of zygote, or pronuclear stage, to the fallopian tube has achieved a higher implantation rate compared with embryos transferred directly into the uterine cavity[2-4]. It was supported by the results in 1994 regenerated from the Society for Assisted Reproductive Technology in the United States showing a pregnancy rate of 29.7 per cent deliveries per retrieval in zygote intrafallopian transfer patients *versus* 20.7 per cent in utrine transfer patients[5]. On the contrary, a prospective comparison within the same clinic demonstrated similar results with uterine (UET) *versus* tubal transfers (TET)[6]. In addition, the study of Balmaceda et al also showed no significant difference in pregnancy rates between tubal and uterine transfers in oocyte donation[7], however, the sample sizes in both studies were small. We postulate that the transfer to the tube should allow a chronologically correct entry of the embryo to the uterine cavity which might improve its chances of implantation[8], whereas the simplicity of the uterine transfer can be at the same time its main limitation in that the precise site of delivery of the embryo can not be controlled. In fact, there is evidence which suggests embryos can be expelled to the vagina[9]. Most IVF programs have returned 2-to 4-cell embryos to the uterus approximately 48 hours after oocyte retrieval[1]. For these reasons, we have used TET in our clinic for quite a while in our clinic instead of GIFT and ZIFT with good results. As the number of TET cases studied worldwide is low, its benefits have never been proved. This study was designed to retrospectively compare the pregnancy rates between TET and UET in our clinic and to evaluate its benefit in certain circumstances.

MATERIAL AND METHOD

Two thousand, seven hundred oocyte retrievals were performed at the Bielefelder Institut fuer Fortpflanzungsmedizin, Bielefeld, Germany from July 1997 to June 1999, 550 of which were TET cases. For each TET case recruited, the next case was UET. Only the patent fallopian tube patients with male infertility, unexplained infertility, mild degree of pelvic adhesion, and minimal pelvic endometriosis were included in the final analysis.

Women were treated with GnRH antagonist (Enantone®) beginning on day 21 of their menstrual cycle followed by FSH (Fertinorm®) on the second day of the subsequent menstrual cycle. Follicular development was monitored with periodic vaginal ultrasounds and serum levels of estradiol. When two or more follicles averaging 17 mm in diameter were found, the patient recieved 10,000 units of hCG. Thirty-six hours later, ultrasound-guided vaginal retrieval of oocytes was performed. Retrieved oocytes were fertilized either conventionally or by intracytoplasmic sperm injection (ICSI) depending on semen quality and fertilization failure. Oocytes were inseminated for 2-4 hours after collection with 150,000 motile sperms per 1 ml for conventional insemination and 1 motile per ooctye for intracytoplasmic sperm injection (ICSI). All oocytes, zygotes, and embryos were cultured in preincubated universal IVF-media (Medi Cult®, Denmark). Dishes were maintained in an incubator with 95 per cent air, 5 per cent CO_2 at 37°C and 100 per cent humidity. Multicell embryos were transferred to the patients with TET or UET approximately 48 hours after oocyte retrieval. No thaw embryos or more than 3 embryos were transferred.

Characteristics of the patients in both groups including age, type of infertility, number of ART treatment cycles, endometrial thickness and estradiol levels at transfer period, number of transferred embryos, degree of pelvic adhesion, and degree of pelvic endometriosis were recorded. Eighteen patients in the TET group and 67 patients in the UET group were excluded from this study due to presence of moderate to severe pelvic adhesion, the presence of moderate to severe pelvic endometriosis, the availability of only one embryo for transfer, and incomplete data.

In total, clinical pregnancy rate and pregnancy outcomes of 1,015 oocyte retrievals with ET were evaluated, 532 in the TET group and

Table 1. The general characteristics of both groups.

	Uterine transfer (N=483)	Tubal transfer (N=532)	p-value
Age (mean±SD)	32.76 ± 4.33	32.88 ± 4.11	NS
No. of ART treatment cycles (mean±SD)	1.98 ± 1.23	2.15 ± 1.16	NS
No. of transferred embryos (mean±SD)	2.64 ± 0.48	2.69 ± 0.46	NS
Endometrial thickness (mean±SD)	10.66 ± 2.04	10.60 ± 1.89	NS
Estradiol levels (mean±SD)	1,549 ± 1,016	1,604 ± 967	NS
No. of primary infertility cases (%)	276 (57.1%)	393 (37.9%)	< 0.000
No. of ICSI cases (%)	275 (56.9%)	444 (83.5%)	< 0.000

483 in the UET group. Patients were determined to be pregnant when a rise in serum hCG concentration was observed on two consecutive occasions 12 days after ET. All clinical pregnancies were confirmed by the presence of an intrauterine sac at sonography. If there was no sac, the pregnancy was considered a chemical pregnancy. Multiple pregnancy was defined by a pregnancy with two or more gestational sacs with fetal heart activity. A diagnosis of ectopic pregnancy was confirmed by laparoscopy. An abortion was defined as pregnancy loss before 20 weeks of gestation.

Statistical Analysis

The data were analyzed using SPSS program and expressed as means with standard deviation (SD). Statistical comparisons were performed with Fisher's exact test, the x^2 test and the t test, and were considered statistically significant at $P < 0.05$.

RESULTS

Table 1 shows the patients' characteristics of both groups (UET and TET). There was no significant difference in the mean age (32.76 *versus* 32.88), number of ART treatment cycles (1.98 *versus* 2.15), number of transferred embryos (2.64 *versus* 2.69), endometrial thickness (10.66 *versus* 10.60) and estrogen levels (1,549 *versus* 1,604) between both groups, whereas the percentages of primary infertility cases and ICSI in the TET group were significantly higher than those in the UET group, 73.9 per cent *versus* 57.1 per cent and 83.5 per cent *versus* 56.9 per cent respectively. Comparing the clinical pregnancy rates between primary and secondary infertility group and between conventional IVF and the ICSI group, we found that there was no significant difference in the pregnancy rates of both groups (27.2% *versus* 30.1% and 26.0% *versus* 29.1% respectively) (Table 2).

Table 2. Pregnancy rate of primary infertility cases and ICSI cases of both groups.

	Uterine transfer (%)	Tubal transfer (%)	p-value
Primary infertilty cases	27.2	30.1	NS
ICSI cases	26.0	29.1	NS

Table 3 shows that the pregnancy rates of the TET group are significantly higher, whereas, the abortion rates are significantly lower than those of the UET group, 31.4 per cent *versus* 24.6 per cent and 12.0 per cent *versus* 23.3 per cent respectively. There are no significant differences of twin, triplet, and ectopic pregnancy rates in both groups (15.0% *versus* 22.8%, 1.7% *versus* 3.6% and 4.2% *versus* 3.0% respectively). However, 4 of 5 ectopic pregnancies in the TET group had evidence of a mild degree of pelvic adhesion and/or a mild degree of pelvic endometriosis.

DISCUSSION

The initial experience with *in vitro* fertilization involved women with tubal disease, but early in the 1980's, the treatment was extended to individuals with male factor infertility, unexplained infertility, endometriosis and immunologic causes for infertility(1). The most recent

Table 3. Results of uterine and tubal transfer.

	Uterine transfer	%	Tubal transfer	%	p-value
No. of cases	483		532		
No. of clinical pregnancies	119	24.6	167	31.4	0.018
No. of singletons	67	55.8	98	58.7	NS
No. of twins	18	15.0	38	22.8	NS
No. of triplets	2	1.7	6	3.6	NS
No. of abortions	28	23.3	20	12.0	0.016
No. of ectopic pregnancies	5	4.2	5	3.0	NS

national statistics from the Society of Assisted Reproductive Technology showed a pregnancy rate for IVF of 20.7 per cent for the year 1994. This poor success rate may be the result of a suboptimal *in vitro* environment as well as our inability to select the best transfer method and the best quality embryos[5]. Some IVF programs suggest that the postponement of embryo transfer from 48 to 72 hours will improve the clinical outcome[10]. The finding that embryos with a higher cell number on either day 2 or day 3 result in a higher pregnancy rate than embryos with fewer cells confirms the reports of many other investigators[11-13]. In contrast, Edwards et al found that delayed embryo transfer (ET) on day 3 had no significant effect on the pregnancy rate when compared with day 2 ET, although the day 3 group had a significantly higher clinical abortion rate than the day 2 ET group[14]. This finding was partly corroborated by van Os et al who also reported no difference in pregnancy rates between day 2 and day 3[15]. In addition, several studies reported no significant effect on the pregnancy or clinical abortion rates when ET was delayed until day 3[16-18]. In a recent large, retrospective study it was reported that day 3 ET did not alter the pregnancy or clinical abortion rates; however, the day 3 group had a significantly higher implantation rate and a lower embryo loss rate than day 2 ET[18]. Most IVF programs in our clinic (about 95%) replaced 2-to 4-cell embryos to the uterus approximately 48 hours after oocyte retrieval. Transfer of more than one embryo increases the chances of pregnancy, but in general no more than 4 or 5 embryos are transferred in order to limit the risk of multiple births.The multiple pregnancy rate with transfer of more than one embryo is approximately 30 per cent (25% twins and 5% triplets or more)[1]. It is comparable to this study (19.5% twins and 2.8% triplets). This risk decreases with advancing age. Thus, in women 40 years old or older it is reasonable to replace a higher number of embryos[1]. However, in our clinic no more than 3 embryos were transferred because by German law, the transfer is limited to no more than 3 embryos and embryos cannot be cryopreserved and transferred in later cycles.

The present study showed that the pregnancy rate of the TET group was significantly higher than that of the UET group (31.4% *versus* 24.6%). We propose that the transfer to the tube allows a chronologically correct entrance of the embryo to the uterine cavity which may improve the chances of implantation(8), whereas the transcervical transfer to the uterine cavity requires the introduction of the catheter that may significantly alter the endometrial milieu and the simplicity of the uterine transfer can, at the same time, be its main limitation in that the precise site of delivery of the embryo cannot be controlled. In fact, there is evidence that suggests embryos can be expelled to the vagina[9]. Although in our study the pregnancy rates achieved through TET are significantly higher than that done through UET (31.4% *versus* 24.6%), both techniques had a similar ectopic rate as previous reports (5 pregnancies or 3% in TET, 5 pregnancies or 4.2% in UET group and 4-5% in previous reports respectively)[1,19]. However, the ectopic pregnancy rate in our TET patients who had no evidence of pelvic adhesion and /or endometriosis may be less because among the 5 ectopic pregnancy cases, 4 had a mild degree of pelvic adhesion and /or mild degree of pelvic endometriosis. The abortion rate in the UET group (23.3%) was comparable

to that of previous reports (about 20%)[1,19], whereas the abortion rate in our TET group was only 12.0 per cent.

Also the importance in terms of choosing a technique is consideration of which program is more comfortable, and which one has achieved the best results. These individual results are more important than countrywide statistics[1]. The additional cost of TET, which requires general anesthesia, an operation and operating room time, may be a deterrent for many individuals. Moreover, anesthesia entails an additional risk that is usually not associated with UET. To decrease the anesthetic risk and post operative pain, and to increase the pregnancy rate, minilaparoscopic TET under local anethesia is a method being considered now in our clinic, so is the assisted hatching technique used for UET. The assisted hatching technigue is associated with an increased implantation rate, especially in older women and patients with repeated IVF failures[1,20]. Nevertheless, we now recommend TET as the first choice for ET in infertile couples with patent fallopian tubes and no evidence of pelvic adhesion and/or endometriosis.

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อัตราการตั้งครรภ์ – การศึกษาเปรียบเทียบย้อนหลังของ TET (การย้ายตัวอ่อนเข้าทางท่อนำไข่) กับ UET (การย้ายตัวอ่อนเข้าทางมดลูกโดยตรง)

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การย้ายตัวอ่อนผ่านเข้าทางท่อนำไข่ (TET) ปัจจุบันยังเป็นที่สงสัยว่าจะให้ผลการตั้งครรภ์ดีกว่าการเคลื่อนย้ายตัวอ่อนเข้าทางมดลูกโดยตรง (UET) หรือไม่ วัตถุประสงค์ของการศึกษานี้เพื่อวิเคราะห์ดูว่าอัตราการตั้งครรภ์ระหว่าง TET และ UET ผู้ป่วยจำนวนทั้งสิ้น 897 ราย ที่เข้ารับการรักษาภาวะมีบุตรยาก ที่ศูนย์ผู้มีบุตรยากของโรงพยาบาล Bielefeld–Rosenhoehe (Bielefelder Institut fuer Fortpflanzungsmedizin, BIF). ระหว่างเดือนกรกฎาคม 2540 ถึงเดือนมิถุนายน 2542 ถูกรวมอยู่ในการศึกษาครั้งนี้ ผู้ป่วยจำนวน 286 ราย มีการตั้งครรภ์ โดยพบว่า 167 ราย (31.4%) เกิดขึ้นภายหลังการรักษาผ่านวิธี TET และ 119 ราย (24.6%) พบว่ามีการตั้งครรภ์ภายหลังการรักษาผ่านวิธี UET นอกจากนี้ยังพบว่าในกลุ่มที่ได้รับการรักษาผ่านวิธี TET มีอัตราการแท้ง 12.0% ขณะที่ในกลุ่มที่ได้รับการรักษาผ่านวิธี UET มีอัตราการแท้งสูงถึง 23.3% จากผลการศึกษานี้แสดงให้เห็นว่าอัตราการตั้งครรภ์ ในกลุ่มที่ได้รับรักษาโดยผ่านวิธี TET สูงกว่าในกลุ่มที่ได้รับการรักษาโดยผ่านวิธี UET อย่างมีนัยสำคัญทางสถิติ และในกลุ่มที่ได้รับการรักษาโดยผ่านวิธี UET และพบว่าการย้ายตัวอ่อนผ่านเข้าทางท่อนำไข่ (TET) ได้รับประโยชน์ในคู่สามีภรรยาที่มีบุตรยากที่ไม่ทราบสาเหตุ หรือมีสาเหตุมาจากฝ่ายชาย ผู้ทำการศึกษาขอแนะนำว่าสมควรให้การรักษาในคู่สามีภรรยาที่มีบุตรยากโดยวิธีย้ายตัวอ่อนผ่านเข้าทางท่อนำไข่ (TET) ในสตรีที่ท่อนำไข่ไม่ตีบตัน ไม่มีหลักฐานแสดงถึงการเกิดภาวะพังผืดในอุ้งเชิงกรานและภาวะเยื่อบุมดลูกเจริญผิดที่

คำสำคัญ : การย้ายตัวอ่อนเข้าทางท่อนำไข่, การย้ายตัวอ่อนเข้าทางมดลูกโดยตรง, การตั้งครรภ์

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