Higher Pregnancy Rate with Intrafallopian Tubal Gamete or Zygote Transfer (GIFT or ZIFT) than Intrauterine Embryo Transfer (IVF-ET)

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Abstracts : From November 1996 to September 1998, we had treated infertile couples who required assisted reproductive conception by allocating to either one of the three treatment methods: IVF-ET for those with bilateral tubal obstruction; ZIFT for those with at least one tubal patency but poor sperm ; and GIFT for those with at least one tubal patency and normal sperm (unexplained infertility). The ovarian stimulation protocol was all the same by using GnRH analogue (Suprefact®) for pituitary suppression and daily hMG (Metrodin®) injection for ovarian stimulation. The oocyte pick up was due when the leading follicle reach 18 mm. For IVF-ET and ZIFT, the fertilization was obtained by conventional in vitro fertilization or by ICSI depending on the sperm quality. Laparoscopic intrafallopian tubal gamete or zygote transfer was preformed on day 0 (ovum pick up day) for the GIFT or on day 1 for the ZIFT group. Intrauterine embryo transfer was performed on day 2- 3 for the IVF-ET group. Every treatment cycle was conducted by the investigator group to minimize the variation of technical bias. Of all the 213 treatment cycles, 82 were IVF-ET, 92 were ZIFT, and 39 were GIFT. The average female patient age in each groups was not different. The pregnancy rate achieved in the GIFT and ZIFT groups were significantly higher than the IVF-ET group (46.2%, 40.2% and 23.2% respectively , $p < 0.05$). For the pregnancy outcome, the abortion rate seemed to be highest in the IVF-ET group (36.8%) whereas the multiple pregnancy rate seemed to be higher in the fallopian tubal transfer group (27% for ZIFT and 38.9% for GIFT), although there were no

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statistical significance. The benefit of the higher pregnancy rate for the intrafallopian tubal transfer treatment group could be due to the more suitable environment for the early stage embryo and the the more synchronize of the endometrial receptivity and the embryo arrival timing provided by the fallopian tube. In conclusion, until the optimal in vitro embryo culture system can be developed, gamete and zygote intrafallopian tubal transfer should yield higher pregnancy rate than intrauterine embryo transfer.

เรื่องย่อ : **อัตราการตั้งครรภ์จากการใส่กลับเซลล์สืบพันธุ์หรือตัวอ่อนทางท่อนำไข่ (GIFT หรือ ZIFT) สูงกว่าการใส่ตัวอ่อนกลับในโพรงมดลูก (IVF- ET)**

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ระหว่างเดือนพฤศจิกายน 2539 ถึงเดือนกันยายน 2541 คู่สมรสที่มีบุตรยากที่มารับการรักษาด้วยวิธีเทคโนโลยีช่วยการเจริญพันธุ์จำนวน 185 คู่ จะได้รับการรักษาด้วยวิธีใดวิธีหนึ่งคือ : IVF-ET ในรายที่ท่อนำไข่อุดตันทั้ง 2 ข้าง, ZIFT ในรายที่ท่อนำไข่อย่างน้อยหนึ่งข้างปกติแต่เชื้ออสุจิผิดปกติ, GIFT ในรายที่ท่อนำไข่และเชื้ออสุจิอยู่ในเกณฑ์ปกติ (ภาวะมีบุตรยากโดยไม่ทราบสาเหตุ) ขั้นตอนเบื้องต้นในการกระตุ้นรังไข่ของทั้ง 3 วิธีจะเหมือนกัน คือ ใช้ desensitizing protocol โดยให้ GnRH analogue ร่วมกับยาฉีด hMG ต่อเนื่องกันทุกวันเป็นระยะเวลาประมาณ 10- 12 วัน ทำการเก็บไข่เมื่อฟองไข่มีขนาดประมาณ 18 ม.ม. โดยใช้เข็มเจาะดูดผ่านทางช่องคลอดอาศัยอุลตราซาวด์เป็นตัวนำ ในรายที่ทำ GIFT จะทำการใส่กลับไข่และเชื้ออสุจิเข้าสู่ท่อนำไข่ในวันที่เก็บไข่ผ่านทางกล้อง Laparoscope ในกรณีที่ทำ ZIFT หรือ IVF-ET จะผสมไข่และเชื้ออสุจิในตู้อบเพื่อให้เกิดการปฏิสนธิเป็นตัวอ่อนก่อน จากนั้นจะใส่กลับตัวอ่อนในระยะ zygote เข้าทางท่อนำไข่ในรายที่ทำ ZIFT หรือเลี้ยงตัวอ่อนต่ออีก 24-48 ช.ม. เพื่อให้ตัวอ่อนแบ่งตัว แล้วจึงใส่กลับเข้าสู่โพรงมดลูกในรายที่ทำ IVF-ET จากการรักษาผู้ป่วยจำนวน 213 cycles โดยเป็น IVF-ET 82 cycles, ZIFT 92 cycles, และ GIFT 39 cycles พบว่าอัตราการตั้งครรภ์ในกลุ่มที่ใส่กลับทางท่อนำไข่ (GIFT และ ZIFT) สูงกว่าในกลุ่มที่ใส่กลับในโพรงมดลูก (IVF-ET) อย่างมีนัยสำคัญ (46.2%, 40.2% และ 23.2% ตามลำดับ, $p < 0.05$) อัตราการแท้งบุตรสูงที่สุดในกลุ่มที่รักษาด้วยวิธี IVF-ET (36.8%) ในขณะที่อัตราการตั้งครรภ์แฝดสูงกว่าในกลุ่มที่ใส่กลับทางท่อนำไข่ (27% ในกลุ่ม ZIFT และ 38.9% ในกลุ่ม GIFT) แต่ไม่พบว่ามีนัยสำคัญทางสถิติ

INTRODUCTION

In natural conception, fertilization of sperm and egg occur in the ampullar part of the fallopian tube. After that, the embryo spents 3-4 days growing in the tube before entering the uterine cavity. The fallopian tube is the natural host of early stage em-

bryo by providing special environment suitable for the embryo to grow. Fallopian tubal mucosa composes of 2 cell types, ciliated and secretory cell, which produce tubal fluid by selective transudation.[1] Study of the oviductal fluid composition found that the concentration of potassium and bicarbonate were higher than in plasma fluid (K^+ 21.2mM vs 5 mM, and HCO^- 35-90mM vs 3.6-5 mM).[1,2] The high K^+ concentration was shown to promote 2-cell mouse embryo development to blastocyst and was claimed to be the principal factor responsible for the higher pregnancy rate of the Human tubal fluid (HTF) over the Tyrode (T6) media for human in vitro fertilization in the Quinn's study.[3] Bicarbonate has the role in stimulation of sperm respiration and motility and is the cofactor of sperm acrosome reaction for the fertilization process. Bicarbonate is also required for embryo development, particularly at the blastocyst stage.[4]

Concerning with the energy substrate in the tubal fluid, the concentration of pyruvate and lactate are high whereas the glucose is low during the midcycle period compare to plasma fluid.[5] Gardner et al[6] believed that this condition should be suitable for the early stage embryo metabolism. Oviduct also secretes certain amino acids which are claimed to help facilitate blastocyst development, improve embryo morphology and hatching rate.[7] Oviduct was found to secrete glycoprotein named Oviductin or Oestrous-associated glycoprotein (EGPs), which is exclusively of oviductal origin.[8] The Oviductin has the role to enhance fertilization and provide embryotrophic activity for the embryo development.[9]

With the more suitable environment as mentioned above, the fallopian tubal transfer of gamete or zygote as GIFT or ZIFT should result in higher pregnancy rate than intrauterine embryo transfer as IVF-ET.

MATERIALS AND METHODS

From November 1996 to September 1998, all the infertile couples who could not achieve pregnancy by natural conception or had been failured from multiple cycles of intrauterine insemination and required the assisted reproductive treatment were recruited in the study. The patients were allocated to either one of the three treatment methods according to the following criteria: IVF-ET for those with bilateral tubal obstruction or severe pelvic adhesion; ZIFT for those with at least one tube was patent but with poor sperm; and GIFT for those with at least one tubal patency and normal sperm (unexplained infertility). The normal contour of uterine cavity and the patency of the fallopian tube was confirmed by hysterosalpingography. Those with tubal obstruction or pelvic adhesion was reconfirmed by diagnostic laparoscopy.

The ovarian stimulation protocol for each treatment group was all the same using desensitizing protocol of GnRH analogue (Suprefact®, Hoechst, Thailand) in associate with daily hMG injection (Metrodin®, Serono, Thailand). The hCG injection was given when leading follicles reach 18 mm. in size. The oocyte pick up was performed 36 hours after the hCG though the vagina under ultrasound guide.

For IVF-ET, the oocytes were fertilized with the sperm by conventional in vitro fertilization method in the culture dish or by intracytoplasmic sperm injection (ICSI) depending on the sperm quality. The embryos were culture for another 24 -48

hours before intrauterine transfer at 4-8 cells stage.

For ZIFT, the fertilization process was the same as the IVF-ET but the embryos were transferred at pronuclear stage on the day of checking fertilization (day1) into the fallopian tube under laparoscope.

For GIFT, the oocytes and washed sperm were transferred onto the fallopian tube on the day of oocyte pick up (day 0) by laparoscope.

Luteal support was given by hCG (1500U) injection on day 2, 6 and 10 after the transfer.

Pregnancy was confirmed by the rising of b-hCG titer (> 50 mU/ml) two weeks after the transfer and the demonstration of intrauterine gestational sac by ultrasonogram another two weeks later.

Every treatment cycle was conducted only by the investigator group to minimize the variation of technical bias.

RESULT

185 infertile couples in 213 treatment cycles were recruited in the study, of which 82 cycles were IVF-ET, 92 cycles were ZIFT, and 39 cycles were GIFT. The average female patient age in each groups were 34.3 (range 21-46) for IVF-ET, 34.8 (range 25-44) for ZIFT and 36.3 (range 26 -45) for GIFT , which were not different . The pregnancy rate achieved in the GIFT and ZIFT groups were significantly higher than the IVF-ET group (46.2%, 40.2% and 23.2% respectively, $p< 0.05$) (Table 1). When broke down into three age groups : < 35 , 35 -39, and > 39 years old; as predicted; the pregnancy rate was mostly lowest in the age group of more than 39 and high in the age less than 35 years old in each treatment group. Although the pregnancy rate of the fallopian tubal transfer group was higher than the intrauterine transfer in all age group, only the group of 35 -39 years old had statistical significance (Table 2). For the pregnancy outcome, the abortion rate seemed to be highest in the IVF-ET group (36.8%) whereas the multiple pregnancy rate seemed to be higher in the fallopian tubal transfer group (27% for ZIFT and 38.9% for GIFT), although there was no statistical significance (Table 3).

DISCUSSION

The results of this study confirmed the higher pregnancy rate of the intrafallopian tubal transfer than intrauterine transfer. Even though the study was not randomized control trial, the outcome was in concert with many other reports.[10,11,12,13] The advantage of the fallopian tubal transfer could be due to two reasons. One is the more suitable environment for the growing embryo, and the other is the more appropiate timing of the embryo arrival into the uterine cavity.[14] Preimplanting embryo can only implant in the endometrium during certain period of the menstrual cycle called " implantation window". In natural conception, the presumed implantation window is around on day 6-10 after the ovulation (day 20-24 of menstrual cycle),[15] which is synchronized with the time of embryo arrival into uterine cavity at the blastocyst stage. In conventional IVF - ET, the embryo transfer is usually performed on day 2- 3 after the ovum pick up at 4 cell stage, which should be too early for the endometrial receptivity and could probably be the reason of the low pregnancy rate. Fallopain tube can provide the more synchronize timing for the embryo arrival and the endometrial receptivity which could bring the higher pregnancy rate. Recently, there have been increasing reports of extend embryonic culture to

Table 1. Pregnancy rate achieved in the three treatment groups

	IVF-ET	ZIFT	GIFT
Average female patient age	34.3 (21 -46)	34.8 (25- 44)	36.3 (26- 45)
No. of transferred cycle	82	92	39
Pregnancy achieved	19	37	18
Pregnancy rate	23.2% *	40.2% *	46.2% *

*p < 0.05

Table 2. Percentage of pregnancy in different age groups

Age group	IVF-ET	ZIFT	GIFT
> 39	0/10 (0%)	2/10 (20%)	1/10 (10%)
35 - 39	9/42 (21.4%)*	11/32 (34.4%)*	9/15 (60%)*
< 35	10/30 (33.3%)	24/50 (48%)	8/14 (57.1%)

*p < 0.05

Table 3. The pregnancy outcome

	IVF-ET	ZIFT	GIFT
Pregnancy achieved	19	37	18
Abortion	7 (36.8%)	6 (16.2%)	4 (22.2%)
Singleton	10 (52.6%)	21 (56.8%)	7 (38.9%)
Multiple pregnancy	2 (10.5%)	10 (27%)	7 (38.9%)

p > 0.05

blastocyst stage and do the transfer on day 5- 6 after the ovum pick up to improve the IVF-ET success rate.[16,17,18] Until the optimal in vitro embryo culture system can be developed, gamete and zygote transfer into the fallopian tube should yield the higher pregnancy rate than the intrauterine embryo transfer.

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