RESEARCH ARTICLE

Gamete intrafallopian transfer versus super-ovulation with intrauterine insemination for the treatment of infertility

A prospective randomised study on pregnancy outcome

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Background. A prospective randomised controlled trial comparing gamete intrafallopian transfer (GIFT) with intrauterine insemination (IUI) was undertaken at the Fertility and Reproductive Biology Unit of the Department of Obstetrics and Gynaecology, Tygerberg Hospital, between July 1999 and June 2000.

Method. Eighty-five women were included in the study and were randomly allocated between the two groups after routine infertility investigations, 41 women to IUI and 44 women to GIFT. A combination of clomiphene citrate and human menopausal gonadotropin was administered to both groups to achieve ovulation.

Results. Six (13.6%) of the 44 cycles in the IUI group and 24 (53.3%) of the 45 cycles in the GIFT group achieved conception. The mean number of cycles needed to achieve pregnancy in IUI was 7.3 (44/6) and in GIFT was 2.05 (45/24). The ongoing pregnancy rate of GIFT was 39.7% more effective than that of IUI (p=0.0001.The total ongoing pregnancy rate of GIFT was 30.8% superior to that of IUI (p=0.0021). When 2 follicles were obtained in an IUI cycle, GIFT was 41.6% more effective (p=0.0024), and when more than 2 follicles were obtained, GIFT was 28.3% more effective (p=0.0265).

Conclusions. The number of mature follicles significantly increased the chance of pregnancy with IUI. In comparing the number of cycles needed to achieve a pregnancy, 1 GIFT cycle is equivalent to more than 3 IUI cycles. It is important to note that 4 IUI cycles will give equivalent or even better results if 2 - 3 follicles are recruited per cycle. In spite of the greater efficacy of GIFT, the authors conclude that at least 3 to 4 IUI cycles should be attempted before GIFT, on the basis that it is more cost effective and less invasive.

Although artificial insemination is one of the oldest and most commonly used infertility treatments, data remain uncertain on the optimal timing of insemination, the number of insertions and the effect of single versus double regimens.[1] The rationale for controlled super-ovulation and intrauterine insemination (IUI) involves the implicit assumption that the ova are being released by the ovary, picked up by the fallopian tubes and that motile sperm reach the ova in concentrations adequate to achieve fertilisation.[2] IUI with or without controlled ovarian hyperstimulation is the treatment entity nearest to the natural form of procreation. It is a less sophisticated procedure, associated with minimum discomfort and trauma, and is essentially more affordable. For these reasons, in many reproductive health care institutions it is often the first line of treatment offered to couples with idiopathic infertility, male factor infertility, and hostile cervical mucus and anti-sperm antibodies.[3]

Gamete intrafallopian transfer (GIFT) was first reported in 1984 by Asch *et al.*[4] as an alternative to *in vitro* fertilisation (IVF), in an attempt to overcome some of the

unaddressed assumptions of IUI. Initially, laparoscopy formed an integral part of the procedure, both in the harvesting of ova and in reintroducing them, combined with sperm, into the fallopian tube. It is a technique aimed at reproducing a physiological step in natural fertilisation and possibly ameliorating the implantation rate of other assisted reproductive technique (ART) programmes. The hypothesis is that the role of the oviduct might not only be mechanical by allowing gamete and embryo transport, but physiological as well, in providing nutrients and other factors important in embryo development. Increased exposures to progesterone and growth factors are some of the most important issues currently being evaluated.[5] Because of the invasive nature of laparoscopy, GIFT has become increasingly unpopular in comparison with other ART, like IVF and intracytoplasmic sperm injection (ICSI). In an attempt to circumvent laparoscopy, techniques such as transvaginal ova aspiration and transcervical GIFT have been evaluated.[6]

In a prospective non-randomised study comparing various ART by Mills *et al.*,[7] the authors observed that the pregnancy rate in GIFT (40%) was the highest, followed by IVF (28%) and IUI (13%). However, the implantation rate per egg transferred by GIFT (21%) was reported to be significantly better than the implantation rate per embryo transferred by IVF (11%). They concluded that the lower pregnancy rates in IUI cycles were to be expected because of limited ovarian stimulation.

The supremacy of GIFT was reaffirmed in a cohort study and meta-analysis by Peterson *et al.*[8] comparing ovulation induction with gonadotropin and IUI to IVF or no therapy. They concluded that the pregnancy rate for one cycle of ovarian stimulation and IUI was inferior to pregnancy rates associated with IVF, GIFT or zygote intra-fallopian transfer (ZIFT). Two cycles were equivalent to IVF or ZIFT but inferior to GIFT. Three cycles were superior to IVF or ZIFT and equivalent to GIFT and four cycles superior to all techniques.

A study by Yovich and Matson[9] also confirmed a significantly better pregnancy rate with GIFT compared with IUI. In contrast to these findings, a prospective study looking at IUI and intraperitoneal insemination, with controlled ovulatory hyperstimulation alone, in comparison with GIFT revealed that IUI was as effective as GIFT. Hogerzeil *et al.*[10] noted no significant difference in pregnancy rate between two GIFT cycles and two ovarian stimulation, IUI cycles.

In an attempt to understand the place and efficacy of various artificial reproductive techniques, we have embarked on a study comparing GIFT and IUI, on the basis of the closer correlation of these two techniques compared with that of other ART techniques such as IVF and ICSI. The aim of this study, therefore, is to compare the pregnancy outcome of IUI and GIFT in a prospective randomised controlled approach.

Materials and methods

During the period 1 July 1999 to 30 June 2000, 85 couples presenting to the Fertility and Reproductive Biology Unit at Tygerberg Hospital with idiopathic infertility were included in a prospective randomised controlled study. All women in the reproductive age group with a minimum duration of infertility of 3 years were included and randomised according to random tables into two groups, namely IUI or GIFT.

Infertility evaluation

Male partner

A semen analysis was performed on the male partner with semen samples obtained at the laboratory after 3 to 4 days of abstinence. The assessment of the sample was done according to the Tygerberg criteria.[11] A spermatozoon was considered normal when the head had a smooth oval configuration and a well-defined acrosome that comprised approximately 40 - 70% of the sperm head. In addition, the sperm should have no neck, midportion or tail defects, and the cytoplasmic droplets should not be larger than one half the size of the sperm head. All morphology groups were accepted into this study. If screening for antibodies had not been done before entry into the programme, a mixed erythrocyte-spermatozoa antiglobulin test (MAR test) was done as a screening procedure to exclude male immunological infertility. The direct immunobead test (DBT) was used to confirm sperm-bound immunoglobulin IgA and IgG.[12]

Female partner

The sperm-cervical mucus contact test was conducted as a screening procedure in all the female patients to exclude a female immunological infertility factor. The indirect immunobead test (IBT) was done to confirm the presence of antibodies in the cervical mucus. Menstrual fluid samples were collected and sent for *Mycobacterium tuberculosis* cultures. Cervical cultures for *Ureaplasma urealyticum* were routinely taken, and if positive, the patient was treated with tetracycline (400 mg 8-hourly for 5 days) before the fertility procedure. A hysterosalpingogram or hysteroscopy and laparoscopy were performed to determine tubal patency and to exclude uterine cavity abnormalities and pelvic adhesions. All patients had an ultrasound scan prior to the treatment offered and the condition of the ovaries and uterus was noted.

Ovarian stimulation

Using a combination of clomiphene citrate and human menopausal gonadotropin, ovarian hyperstimulation was achieved in all patients.[13] Patient follow-up consisted of serum luteinising hormone and estradiol determinations, as well as serial ultrasonographic

measurement of the graafian follicle and endometrial thickness. Human menopausal gonadotropin (hMG) was administered as soon as the leading follicle reached a diameter of 18 mm. Follicle aspiration was performed 36 hours later.

In the case of the IUI cohort, 50 mg of clomiphene citrate was administered from day 4 to day 8 of each cycle, with one ampoule of hMG on days 4, 6 and 8.

In the GIFT cohort the clomiphene citrate dose was 100 mg per day, with two ampoules of hMG administered every alternate day starting on the 4th day of the cycle.

Semen preparation

On the day of the GIFT/IUI procedure (36 - 42 hours after hMG administration), the spouse was asked to produce a semen sample 1½ hours before laparoscopy/ IUI. The semen was prepared according to the double wash and swim-up technique.[14]

Gamete intrafallopian transfer

Laparoscopy and follicle aspiration was performed under general anaesthesia. One hundred per cent CO_2 was used to create the pneumoperitoneum. The aspirated oocytes were evaluated for maturity and classified according to the criteria described by Veeck[15] as being either metaphase I or II. Three oocytes were randomly selected on completion of follicle aspiration. Patients in whom less than 3 oocytes were obtained during aspiration were excluded from the study. Oocytes were loaded into the transfer catheter together with 100 000 sperm. The number of sperm was increased to 500 000 if the male partner had a morphology of less than 14% normal forms on semen analysis.[16] The loaded catheter was passed through the cannula used for aspiration and then inserted into the fallopian tube up to a distance of 2 cm from the fimbrial opening, where the gametes were deposited. All excess oocytes were fertilised in vitro and embryos were frozen at the eight-cell stage for future replacement.

Intrauterine insemination

Patients with more than 3 follicles were excluded from the study. Inseminations were performed with an Edwards-Wallace Embryo Replacement Catheter® (Simcare and SIMS ref. 1816). The inseminate, suspended in 1 ml of standard medium, was slowly injected high up into the uterine cavity. The patient rested for 10 minutes before resuming normal activity.

Diagnosis of pregnancy

The conception rate in this study included all biochemical pregnancies and conception was diagnosed if the serum β-hCG was positive on day 12 and if the values had doubled on day 16 after insemination. The ongoing pregnancy rate was defined as the number of pregnancies that reached a viable gestational age of 28 weeks.

Statistical analysis

In an intention-to-treat analysis, the conception rate and the ongoing pregnancy rate in the two arms of the trial were compared by means of Fisher's exact test for the difference in proportions. The absolute difference between the proportions was estimated as well as the 95% confidence intervals (CIs) for reporting the effect size of the trial.

The conception rate in specific subgroups relating to the number of follicles observed in the IUI arm was also compared to the GIFT arm with Fisher's exact test. The analysis was done using the statistical analysis system (SAS).[17]

The easiest way to correlate the two entities is in the number needed to treat (NNT), in this case the number of cycles to attain pregnancy.

Results

The mean age of the female partners in the IUI group was 32 years (range 27 - 38 years). The total number of women involved was 41 and a total number of 44 cycles was attempted. The conception rate achieved with IUI was 13.6% (6/44) and the ongoing pregnancy rate per cycle was 6.8% (3/44). The conception rate with 2 follicles per cycle was 11.8% (2/17), and with more than 2 follicles per cycle the rate was 25% (4/16). No pregnancies resulted when a single follicle per cycle was achieved. There was one tubal pregnancy and 5 intrauterine pregnancies, of which 4 were singleton pregnancies and 1 multiple. Three of the intrauterine singleton pregnancies resulted in 2 female babies and 1 male baby, while the twins and the other singleton pregnancy aborted at 16 and 8 weeks' gestation respectively. The rate of twinning was 1/6 (16.7%), the miscarriage rate was 2/6 (33.33%) and the rate of tubal pregnancies was 1/6 (16.7%) (Table I).

In the GIFT group, the mean age of the female partners was 34 years (22 - 40). The total number of women involved was 44 and a total of 45 cycles were attempted. The conception rate achieved with GIFT was 53.3% (24/45), and the ongoing pregnancy rate per cycle was 35.6% (16/45). There were 23 intrauterine pregnancies and 1 tubal pregnancy. Among the intrauterine pregnancies, there were 3 sets of twins and 13 singletons (a total 19 babies, 8 females and 11 males). The rate of twining was 12.5% (3/24), the miscarriage rate was 19.17% (7/24) and the rate of tubal pregnancies was 4.17% (1/24) (Table II).

To correlate the two entities we used number needed to treat (NNT) to achieve a pregnancy and the effect size as an estimation of efficacy between the two entities.

The number of cycles needed to achieve pregnancy in IUI was 7.3 (44/6) and in GIFT it was 2.05 (45/24). It can therefore be concluded that on average one would need 5 extra IUI cycles to compare to 2 GIFT cycles to achieve pregnancy. Looking at the relationship between GIFT

Table I. Pregnancy rate according to the number of follicles achieved with IUI

No. of follicles	Conception rate per cycle		Ongoing pregnancy rate (>28 wks)	
1	0/11	(0%)	0/11	(0%)
2	2/17	(11.8%)	1/17	(5.9%)
>2	4/16	(25%)	2/16	(8%)
	6/44	**(13.6%)**	**3/44**	**(6.82%)**
	Subdivision of pregnancies			
	Singletons born	**Sets of twins born**	**Miscarriages**	**Tubal**
Pregnancy outcome	3/6 (50%)	0/6 (0%)	2/6 (33.3%) 1 singleton 1 set twins	1/6 (16.7%)

Table II. Pregnancy rate achieved with GIFT

No. of women	Conception rate per cycle		Ongoing pregnancy rate (>28 wks)	
44	24/45	(53.3%)	16/45	(35.6%)
	Subdivision of pregnancies			
	Singletons born	**Sets of twins born**	**Miscarriages**	**Tubal**
Pregnancy outcome	13/24 (54.17%)	3/24 (12.5%)	7/24 (29.17%)	1/24 (4.17%)

and IUI (7.3/2.05=3.6), 1 GIFT cycle would therefore be proportional to 3.6 IUI cycles.

The effect size, as illustrated in Table III, is an indicator of how much more effective GIFT is in comparison with IUI. The ongoing pregnancy rate of GIFT is 39.7% more effective than that of IUI, with a *p*-value of 0.0001, and the total ongoing pregnancy rate is 30.8% more superior to that of IUI, with a *p*-value of 0.0021. When 2 follicles were achieved in an IUI cycle, GIFT was 41.6% more effective (*p*-value 0.0024) and when more than 2 follicles were achieved, GIFT was 28.3% more effective (*p*-value 0.0265) (Table III).

Discussion

Despite the large amount of published information on the topic of assisted reproduction there are surprisingly few data from well-planned prospective randomised investigations. Although results published from such studies often proclaim the superiority of a particular technique, the proliferation of uncontrollable and sometimes unknown confounding variables suggests that the findings should be viewed with caution. On the relatively few occasions when a more rigorous approach has been followed, it is surprising how difficult it has been to produce evidence of the differential efficacy of the assisted reproduction methods in current use.[18]

We therefore embarked on a study of comparing IUI and GIFT in a prospective randomised controlled approach, on the basis of the closer relationship of these two techniques compared with that of IVF. The hypothesis was that the role of the oviduct might not only be mechanical by affording gamete and embryo transport, but probably has a physiological role in providing nutrients and other factors important in embryo development.[5]

Many earlier studies have confirmed the superiority of the GIFT procedure over all assisted reproductive methods in couples where there is unexplained and male-related subfertility but evidence of normal fallopian tubes.[7,11,19-23] In contrast, the retrospective analysis by Dodson *et al.*[24] showed that super-ovulation with intrauterine insemination approached the fecundity of normal women, and equalled or exceeded that reported for IVF-ET and GIFT. However, all authors recommended randomised controlled trials to compare and demonstrate the efficacy of super-ovulation with intrauterine insemination and GIFT procedures and favour attempts at IUI before the more invasive and expensive procedures of ART.

The relationship between GIFT and IUI revealed that one GIFT cycle would be proportional to 3.6 IUI cycles. This compares well with a cohort study and meta-analysis by Peterson *et al.*[8] comparing ovulation induction with gonadotropin and IUI, to IVF or no therapy. They concluded that the pregnancy rate for one cycle of (hMG) ovarian stimulation and IUI was inferior to pregnancy rates associated with IVF, GIFT or ZIFT; 2 IUI cycles were equivalent to IVF or ZIFT but inferior to GIFT, 3 cycles were superior to IVF or ZIFT and equivalent to GIFT and 4 cycles were superior to all techniques. The conclusion was therefore made that at

Table III. Effectiveness of GIFT in comparison with IUI as illustrated in effect size and its associated power

Gift v. IUI	Effect size (95% CI)	*p*-value
Conception rate	39.7% (20.4 - 55.2%)	0.0001
Ongoing pregnancy rate	30.8% (12 - 46.9%)	0.0021
>2 follicles	28.3% (0 - 48.5%)	0.0265
2 follicles	41.6% (14.9 - 57.7%)	0.0024

least 4 cycles of IUI are indicated before embarking on the application of more advanced assisted reproductive techniques, and we support this statement based on the data represented in our study.

An additional important finding of this study was that the pregnancy rate in the IUI procedure significantly improved as the number of mature follicles increased. The pregnancy rate with 2 follicles per cycle was 11.8% and the pregnancy rate with more than 2 follicles per cycle was 25% for these subgroups. No pregnancies resulted when a single follicle per cycle was achieved. The difference was still significant in favour of GIFT, in terms of pregnancy outcome, independent of the number of follicles achieved in IUI (Table III). This finding should motivate clinicians to try to achieve well-controlled ovulation induction with 2 but not more than 4 follicles to achieve maximum benefit from IUI attempts. There was no statistical significance between the two groups regarding the miscarriage rate, rate of tubal pregnancies and rate of multiple pregnancies.

In conclusion, this prospective randomised controlled clinical trial has demonstrated that GIFT is superior to IUI in relation to pregnancy outcome. However, it is important to note that 4 IUI cycles will give equivalent or even better results if 2 - 3 follicles are recruited per cycle. In view of the fact that IUI is a non-invasive procedure, it should be strongly considered as a first-line approach in the management of selected infertile couples.

1. Alborzi S, Motazedian S, Parsanezhad ME, Jannati S. Comparison of the effectiveness of single intrauterine insemination (IUI) versus double IUI per cycle in infertility patients. *Fertil Steril* 2003; 80: 595-599.
2. Guzick DS, Sullivan MW, Adamson GD, *et al.* Efficacy of treatment for unexplained infertility. *Fertil Steril* 1998; 70: 207-213.
3. Waardt J, Kruger TF, Lombard CJ, Ombelet W. Predictive value of normal sperm morphology in intrauterine insemination (IUI): a structured literature review. *Hum Reprod* 2001; 7: 495-500.
4. Asch RH, Balmaceda JP, Ellsworth LR, Wong PC. Gamete intrafallopian transfer (GIFT): a new treatment for infertility. *Int J Fertil* 1985; 2: 1034.
5. Hannoun A, Abu-Musa A. Gamete intrafallopian transfer (GIFT) in the treatment of severe male infertility. *Int J Gynaecol Obstet* 1998; 61: 293-295.
6. Sallam HN, Agamia AF, Sallam AN, Ezzeldin F. Transcervical gamete intrafallopian transfer versus controlled ovarian hyperstimulation and intrauterine insemination in the treatment of unexplained infertility. *Fertil Steril* 1997; 68: 72-73.
7. Mills MS, Eddowes HA, Cahill DJ, *et al.* A prospective controlled study of in vitro fertilization, gamete intrafallopian transfer and intrauterine insemination combined with super ovulation. *Hum Reprod* 1992; 7: 490-494.
8. Peterson CM, Hatasaka HH, Jones KP, *et al.* Ovulation induction with gonadotropins and intrauterine insemination compared with *in vitro* fertilization and no therapy: a prospective non-randomized, cohort study and meta-analysis. *Fertil Steril* 1994;62: 535-544.
9. Yovich JL, Matson PL. Pregnancy rate after high intrauterine insemination of husband's spermatozoa or gamete intrafallopian transfer. *Lancet* 1986; 2: 1287.
10. Hogerzeil HV, Spiekerman CM, De Vries JWA, *et al.* A randomized trial between GIFT and ovarian stimulation for the treatment of unexplained infertility and failed artificial insemination by donor. *Hum Reprod* 1992; 7: 1235.
11. Kruger TF, Menkveld R, Stander FSH, *et al.* Sperm morphologic features as a prognostic factor in, *in vitro* fertilization. *Fertil Steril* 1986; 46: 1118-1123.
12. Menkveld R, Stander FSH, Kotze TJ, Kruger TF, van Zyl JA. The evaluation of morphological characteristics of human spermatozoa according to the stricter criteria. *Hum Reprod* 1990; 5: 589-592.
13. Van Der Merwe JP, Kruger TF, Swart Y, Lombard CJ. The role of oocyte maturity in the treatment of infertility because of teratozoospermia and normozoospermia with gamete intrafallopian transfer. *Fertil Steril* 1992; 58(3): 581-586.
14. Kruger TF, Acosta AA, Simmons K, Swansons RJ, Matta J, Oehninger S. Predictive value of abnormal sperm morphology *in vitro* fertilization. *Fertil Steril* 49: 112-117.
15. Veeck LL. Abnormal morphology of the human oocyte and conceptus. In: *Atlas of the Human Oocyte and Early Conceptus.* New York: Parthenon Publishing, 1999: 57-68.
16. Oehninger S, Acosta AA, Morshedi M, *et al.* Corrective measures and pregnancy outcome *in vitro* fertilization in patients with severe sperm morphology abnormalities. *Fertil Steril* 1988; 50: 283-287.
17. SAS Institute Inc. SAS/STAT Users Guide, Version 8. Cary, NC: SAS Institute Inc., 1999. www.sas.com
18. Crosignani PG, Walters GE, Soliani A. The ESHRE multicenter trial on the treatment of unexplained infertility: a preliminary report. *Hum Reprod* 1991; 6: 963-968.
19. Kenny DT. *In vitro* fertilization and gamete intrafallopian transfer: an integrative analysis of research, 1987-1992. *BJOG* 1995; 102: 317-325.
20. Leeton J, Rogers P, Caro C, Healey D, Yates C. A controlled study between the use of gamete intrafallopian transfer (GIFT) and *in vitro* fertilization and embryo transfer in the management of idiopathic and male infertility. *Fertil Steril* 1987; 48: 605-612.
21. Tanbo T, Dale PO, Abyholm T. Assisted fertilization in infertile women with patent fallopian tubes. A comparison of *in vitro* fertilization, gamete intrafallopian transfer and tubal embryo stage transfer. *Hum Reprod* 1990; 5: 266-270.
22. Ranieri M, Becket VA, Marchant S, *et al.* Gamete intrafallopian transfer or in vitro fertilization after failed ovarian stimulation and intrauterine insemination in unexplained infertility. *Hum Reprod* 1995; 10: 2033-2036.
23. Abyholm T, Tanbo T, Date PO, *et al. In vitro* fertilization procedures in infertile women with patent fallopian tubes: a comparison of gamete intrafallopian transfer, combined intrauterine and intraperitoneal insemination and controlled ovarian hyperstimulation alone. *J Assist Reprod Genet* 1992; 9:19-23.
24. Dodson WC, Whitesides DB, Hughes CL Jr, Early HA 3d, Haney AF. Super ovulation with intrauterine insemination in the treatment of infertility: a possible alternative to gamete intrafallopian transfer and in vitro fertilization. *Fertil Steril* 1987; 48(3): 441-445.

Alternative?

A Dutch doctor has been struck off the medical register for treating a patient with breast cancer by alternative care. An actor and comedian, Sylvia Millecam had a lump in her breast diagnosed as cancer. It measured 3 - 4 cm but she did not want conventional treatment, so the doctor in question used magnetic field therapy and other alternative cures for 6 months, by which time the tumour had more than doubled in size. She died in less than a year.

He argued that if he had insisted on oncological treatment his patient would have been 'lost' to follow-up. He kept inadequate notes and prevented her from having mainstream medical opinion. He was originally given a 6-month suspended sentence but appealed, only to be struck off the medical register for life (Sheldon, *BMJ* 2007; 335: 13).