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The treatment of normospermic infertility by gamete intrafallopian transfer (GIFT)

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Summary. Gamete intrafallopian transfer (GIFT) was applied in 207 treatment cycles in 73 couples. The pregnancy rate in cycles with only one (2/21, 9·5%) or two (2/29, 6·9%) oocytes transferred was significantly less than that in which four oocytes (36/116, 31·0%) were replaced. The collection of more than four oocytes did not influence the pregnancy rate in that treatment cycle. The overall pregnancy rate was 24·2% (50 of 207) and was similar in the four infertility groups studied (non-occlusive tubal disorders, endometriosis, cervical factor and unexplained infertility) with 28 (56%) of the pregnancies delivered at ≥20 weeks. The pregnancy wastage included 4 (8%) ectopic pregnancies and 3 (6%) late pregnancy losses. The 12 multiple pregnancies occurred following the transfer of three and four oocytes.

Many therapeutic techniques are now available for the treatment of infertile couples in which the female partner has patent fallopian tubes. Those procedures involving the manipulation of gametes include artificial insemination with husband's spermatozoa (AIH) whereby spermatozoa are deposited in the cervical canal or uterus (Allen *et al.* 1985), the placing of oocytes and spermatozoa into the uterus to allow fertilization to occur *in vivo* (Craft *et al.* 1982), and conventional in-vitro fertilization and embryo transfer (IVF-ET) in which fertilization occurs extracorporeally with subsequent transfer of embryos into the uterus (Edwards & Purdy 1982).

A procedure proving particularly successful is gamete intrafallopian transfer (GIFT), whereby oocytes and spermatozoa are transferred into the fallopian tubes. Since the first report (Asch *et al.* 1984), GIFT seems to give similar results at most centres using the technique (Guastella *et al.* 1985; Asch *et al.* 1986; Corson *et al.* 1986; Molloy *et al.* 1986; Nemiro *et al.* 1986; Yovich *et al.* 1986) and pregnancy rates of the order of 30 per 100 treatment cycles can be achieved for normospermic couples (Asch 1986).

The present study describes the results of the GIFT programme at PIVET Medical Centre and the principal aims were to determine: the pregnancy outcomes in relation to the underlying infertility aetiology; the effect of transferring different numbers of oocytes on the pregnancy rates; whether pregnancy rates are improved by hyperstimulation as gauged by the number of oocytes collected; the outcome of pregnancies achieved following GIFT; and the relation

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between the number of oocytes transferred and the frequency of multiple pregnancies.

Subjects and methods

The study was undertaken at the PIVET Medical Centre and was based on the first 207 GIFT treatment cycles in 73 couples without any recognizable male factors. All male partners were normospermic, the ejaculates containing $\geq 12 \times 10^6$ motile spermatozoa/ml (Yovich *et al.* 1985*a*). Couples with antispermatozoal antibodies either in male semen or in female serum were not included. Each woman had at least one fallopian tube shown to be patent and mobile at laparoscopy. Underlying tubal damage was known to be present in 22 women, a further 13 women had endometriosis graded according to classification published by the American Fertility Society (1985), 16 had a suspected cervical factor because of negative postcoital tests (Matson *et al.* 1986) and 22 women had completely unexplained infertility.

All women in this study had follicular growth stimulated by clomiphene citrate (Clomid, Merrell-Dow Pharmaceuticals, Inc.), human menopausal gonadotrophin (hMG; Pergonal, Serono) or a combination of both. The response to treatment was monitored daily from day 2 of the menstrual cycle by radioimmunoassay of serum oestradiol-17β, progesterone and luteinizing hormone (LH) levels, and from day 8 of the cycle using ultrasound. Ovulation was triggered by the occurrence of an endogenous LH surge or the administration of 10 000 i.u. human chorionic gonadotrophin (hCG; Primogonyl, Schering) at an appropriate time (Yovich *et al.* 1985*b*) and oocytes were collected approximately 35 h later via laparoscopy or an ultrasonically guided needle.

Husbands produced a semen sample by masturbation 2 h before the oocyte collection. Motile spermatozoa were then isolated using the swim-up technique employed in the IVF programme (Yovich & Stanger 1984). The final suspension of motile spermatozoa was adjusted to 2000/μl. The culture medium used was human tubal fluid (HTF) medium (Quinn *et al.* 1985) supplemented with 20% heat-inactivated serum.

Once oocytes had been collected, the gametes were transferred to the fallopian tube at laparoscopy. The GIFT catheter was a 50-cm-long 16-gauge end-hole Teflon catheter (William Cooke, Australia). The catheter was then loaded with: (a) HTF medium with 20% serum to fill the dead space; (b) 5 μl air; (c) 25 μl of medium with oocytes; (d) 5 μl air; (e) 50 μl of spermatozoal suspension; (f) 5 μl air.

The fallopian tube was then catheterized (Molloy *et al.* 1986) and the gametes were transferred. Patients were allowed to go home after they recovered from anaesthesia and were free to carry on normal activities, including work and sexual relations. Pregnancies were diagnosed by an elevated serum β-hCG level on or after day 16 of the luteal phase and eventually categorized according to the criteria published by Yovich & Matson (1988) as a biochemical pregnancy (falling hormone levels and no detectable gestational sac on ultrasound), blighted ovum (gestational sac at 7 weeks without a clear fetus and fetal heart action), miscarriage (fetal loss after ultrasound detection of fetal heart movement) and late pregnancy loss (fetal or neonatal death after 20 weeks gestation).

The χ^2-test was applied for statistical analysis in contingency tables.

Results

The pregnancy rates achieved after GIFT were similar in the four categories of infertility treated (Table 1), the overall rate was 24·2% (50 in 207 cycles). However, the pregnancy rates were markedly influenced by the number of oocytes transferred into the fallopian tubes ($\chi^2 = 9{\cdot}37$, df = 3, $P<0{\cdot}025$). A comparison of individual groups using 2 × 2 contingency tables showed that the pregnancy rates were significantly lower in cycles when only one (2/21; $\chi^2 = 4{\cdot}10$, $P<0{\cdot}05$) or two (2/29; $\chi^2 = 6{\cdot}99$, $P<0{\cdot}01$) oocytes were transferred than when four oocytes were transferred (36/116). The number of pregnancies achieved in women in whom ovulation was triggered by an endogenous LH surge was particularly low when three or fewer oocytes were replaced (one pregnancy in 27 cycles) although the numbers are too small to allow reliable statistical analysis.

Among the women who had four oocytes transferred, the pregnancy rates did not differ between those from whom more than four oocytes were collected (26/87; 29·9%) and those with only four oocytes collected (10/29, 34·5%; $\chi^2 = 0{\cdot}22$).

The pregnancy outcome achieved after GIFT is given in Table 4. Of the 50 pregnancies achieved, 28 (56%) continued to delivery

Table 1. Pregnancy rates achieved after GIFT

	No. women	No. cycles	Pregnancies	Pregnancy rate/cycle
Tubal damage:				24·2%
Previous tubal surgery	13	37	10	
PID adhesions	9	25	5	
Endometriosis:				26·5%
Stage I	6	16	5	
Stage II	4	13	2	
Stage III	2	4	1	
Stage IV	1	1	1	
Cervical factor	16	39	10	25·6%
Unexplained	22	72	16	22·2%
Totals	73	207	50	24·2%

PID, Presumptive diagnosis of previous pelvic inflammatory disease.
Endometriosis classified according to American Fertility Society (1985) classification.

Table 2. Pregnancy rates according to the number of oocytes transferred

Ovulatory trigger	No. oocytes transferred								Total	
	1		2		3		4			
LH surge	0/8		0/5		1/14		9/26		10/53	(18·9%)
hCG	2/13		2/24		9/27		27/90		40/154	(26·0%)
Total	2/21	(9·5%)*	2/29	(6·9%)*	10/41	(24·4%)	36/116	(31·0%)	50/207	(24·2%)

*$P<0·05$ compared with four oocytes transferred.

beyond 20 weeks. Two twin pregnancies ended in miscarriage at 12 and 14 weeks gestation and one woman in whom eight sacs and seven fetal hearts were detected miscarried at 18 weeks. This patient had four oocytes transferred. Four fetuses were terminated selectively by ultrasound-guided needling at 9 weeks (Mulcahy *et al.* 1984) but the remaining triplet pregnancy ended in miscarriage in the 18th week. We were unable to determine if the eight sacs were derived from duplication of the four oocytes or whether further spontaneous ovulation occurred after the GIFT procedure. Late pregnancy loss occurred in two twin pregnancies with fetal death at 23 and 24 weeks respectively, and in one singleton pregnancy at 24 weeks. Four ectopic pregnancies occurred in women with a history of surgery for tubal disease (4/37; 10·8%), suggesting that this group of patients is at particular risk.

The frequency of multiple pregnancies in relation to the number of oocytes transferred is shown in Table 5. The number of gestational sacs with fetal heart beats was recorded on the first obstetric ultrasound echogram at 7 weeks, and therefore includes the miscarriages and late pregnancy losses mentioned above. There is a clear trend in the frequency of multiple gestational sacs with the transfer of increasing numbers of oocytes. Specifically, 100% (3/3) triplet pregnancies resulted from the transfer of four oocytes; 75% (6/8) and 25% (2/8) twin pregnancies were diagnosed in women who had four and three oocytes transferred.

Discussion

Experience of IVF-ET suggests that the pregnancy rate increases when the number of embryos replaced is increased (Osborn & Moor 1985). The present study has demonstrated a similar phenomenon with GIFT when increasing numbers of oocytes are transferred, with rates being maximal when three or four oocytes are replaced. This pattern is parallel to that described recently from a multi-centre study (Asch 1986) in which pregnancy rates of 4%, 19%, 44% and 41% were obtained from a total series of 800 cases when 1, 2, 3 or 4 oocytes were transferred. Such a trend is not always seen, and Nemiro & McGaughey (1986) found no association between the pregnancy rate and the number of oocytes replaced at GIFT. They obtained pregnancy rates of 40%, 29%, 21% and 46% after the transfer of 1, 2, 3 and 4

Table 3. Pregnancy rates after transfer of four oocytes according to the number of oocytes collected

Ovulatory trigger	No. oocytes collected								Total	
	4	5	6	7	8	9	10	≥10		
LH surge	2/10	2/7	1/3	2/4	1/1	—	—	1/1	9/26	(34·6%)
hCG	8/19	4/17	5/18	5/11	1/4	2/9	0/4	2/8	28/90	(30·0%)
Total	10/29 (34·5%)	6/24 (25·0%)	6/21 (28·6%)	7/15 (46·7%)	2/5 (40·0%)	2/9 (22·2%)	0/4 (—)	3/9 (33·3%)	36/116	(31·0%)

oocytes. It is also apparent from the present study that the pregnancy rates, when three or fewer oocytes were transferred, were reduced when ovulation was triggered by an endogenous LH surge. This may be due to the immaturity of the transferred oocytes because of the difficulty in determining accurately the time of the onset of the LH surge by the analysis of daily blood samples. No difference in fertilization or pregnancy rates has been found in our IVF programme between oocytes collected following an LH surge or hCG injection (unpublished data), although this may be explained by the delayed insemination of oocytes (Trounson *et al.* 1982) as routinely practised, allowing any immature oocytes to complete the maturational process (Osborn & Moor 1985) in culture. The possibility of performing IVF-ET or pronuclear stage tubal transfer (PROST) (Yovich *et al.* 1987) in those women with ≤3 oocytes and ovulation triggered by an endogenous LH surge requires further consideration. If maturity of the oocytes is a problem, then their pre-incubation for IVF-ET or PROST should be beneficial.

Table 4. Pregnancy outcome in patients who conceived after GIFT

Pregnancy outcome	No. pregnancies	%
Delivered at ≥20 weeks	28	(56%)
Biochemical	6	(12%)
Blighted ovum	6	(12%)
Miscarriage	3	(6%)
Ectopic	4	(8%)
Late pregnancy loss	3	(6%)
Total	50	(100%)

Table 5. Frequency of multiple pregnancies diagnosed at 7 weeks by ultrasound, according to the number of oocytes transferred

Pregnancy	No. oocytes transferred				Total
	1	2	3	4	
Singleton	—	2	6	14	22
Twins	—	—	2	6	8
Triplets	—	—	—	3	3
>3 sacs	—	—	—	1	1
Total	—	2	8	24	34

The present study has shown that the stimulation of follicular growth to the extent that supernumerary oocytes are recovered does not increase the chance of pregnancy in that particular treatment cycle. This is of interest because studies on IVF-ET have demonstrated that higher serum progesterone concentrations in the early luteal phase are associated with the establishment of pregnancy (Garcia *et al.* 1984; Yovich *et al.* 1985*c*). This, coupled with the observation that the aspiration of follicles removes granulosa cells and disrupts progesterone secretion in some patients (Garcia *et al.* 1981; Frydman *et al.* 1982), might suggest that increased numbers of follicles would help maintain luteal phase progesterone concentrations and confer some benefit. Whilst not affecting the pregnancy rate per treatment cycle, the fertilization *in vitro* of supernumerary oocytes and the subsequent cryopreservation of embryos can increase the chance of pregnancy per oocyte collection by enabling women to have the transfer of a thawed embryo or embryos at a later date (Mohr *et al.* 1985).

The present series does not include male factor infertility. We did explore this area and found a need to develop a modified GIFT technique to achieve pregnancies (Matson *et al.* 1987). We also avoided GIFT in cases where either partner had antispermatozoal antibodies because one of the limitations of GIFT is that the procedure does not allow the confirmation of fertilization in couples who do not conceive. This may eventually become possible when the platelet agglutinating factor (PAF) test is fully developed and becomes available (O'Neill *et al.*

1987). The use of supernumerary oocytes as an in-vitro test of fertilization is not useful as a determinant of fertilization *in vivo*, since pregnancies can be achieved when the supernumerary oocytes fail to fertilize (Matson *et al.* 1987). In the groups of patients treated here (unexplained infertility, non-occlusive tubal damage, endometriosis and cervical factor) the chance of pregnancy was equivalent and the technique of GIFT appears equally indicated. However, those cases with a severe male factor, antispermatozoal antibodies and a poor history with repeated failures to conceive in the GIFT programme are best treated by the PROST method (Yovich & Matson 1988). At the PIVET Medical Centre, the technique of IVF-ET is now reserved for cases of irremediable tubal occlusion or in non-occlusive tubal disease where neither fallopian tube can be mobilized satisfactorily for successful cannulation in the GIFT and PROST procedures. Of course, it can be argued that many patients with patent fallopian tubes will conceive and do not need IVF, GIFT or PROST treatments. But the spontaneous rate of conception in such patients on the waiting list is of the order of only 5% per annum (unpublished observations). Clearly GIFT treatment enhances fertility, such that if each case could be treated up to three times per annum, more than 70% would have conceived. It may also be considered that only the transfer of oocytes to the fallopian tubes is necessary in those patients who demonstrate satisfactory postcoital tests. This may well be the case and requires further study as relevant data were not generated in this series.

There was a clear association between the frequency of multiple pregnancies and the increasing number of oocytes transferred, in agreement with Nemiro & McGaughey (1986) who reported more triplet and quadruplet pregnancies when four oocytes were transferred. In view of the similar pregnancy rate in this study and elsewhere (Asch 1986) when three or four oocytes are replaced, consideration should be given to limiting the number of oocytes transferred to three. This may also have the benefit of reducing the frequency of multiple pregnancies. One of our patients had seven gestational sacs with fetal pulse activity detected following the transfer of only four oocytes. Although the precise reason for this remains unknown, possibilities include multiple monozygotic twins or delayed ovulation from a secondary cohort of follicles.

The high ectopic pregnancy rate (6%) is not greater than that observed in subfertile patients conceiving after other treatments, including ovarian stimulation, intrauterine insemination with husband's washed sperm, IVF or after reconstructive tubal microsurgery (Yovich & Matson 1988). All cases in this series occurred in patients with known non-occlusive tubal diseases but the rate (4/98; 4·1%) is not excessive for this group and even the rate of 10·8% in women who had previous reconstructive surgery should not preclude GIFT as a treatment option for those who fail to conceive readily after tubal repair where at least one tube remains patent.

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